CERTIFICATE OF TRANSLATION

I, Haruko MIWA, am a patent attorney of ION PATENT of Hayakawa-Tonakai Bldg. 3F, 12-5, Iwamoto-cho 2-chome, Chiyoda-ku, Tokyo, Japan, do solemnly and sincerely declare that I am conversant with the Japanese and English languages and I have executed with the best of my ability this translation into English of Japanese Patent Application No. 10-311491 attached hereto which was filed on October 30, 1998 in the name of Hidemitsu NISHIDA et al./MOCHIDA PHARMACEUTICAL CO., LTD. and believe that the translation is true and correct.

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Haruko MIWA
Patent Attorney

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[TITLE OF THE INVENTION] AROMATIC COMPOUNDS HAVING CYCLIC AMINO GROUPS AND SALTS THEREOF

[NUMBER OF CLAIMS] 9

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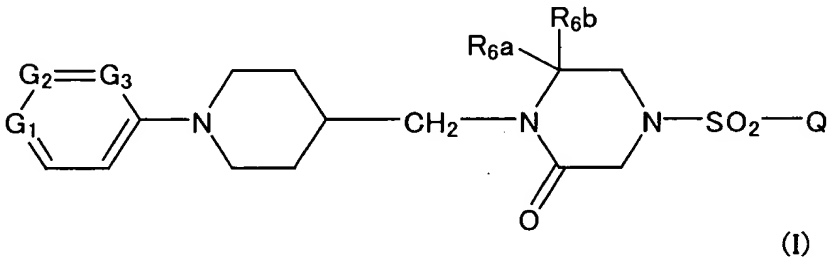
[TITLE OF THE INVENTION] AROMATIC COMPOUNDS HAVING CYCLIC AMINO GROUPS AND SALTS THEREOF

[CLAIMS]

[Claim 1]

A compound represented by the following formula (I) or a salt thereof:

[Chemical Formula 1]



(I)

(wherein G_1, G_2 and G_3 are independently CH or N, provided that at least one of them is N;

one of R_{6a} and R_{6b} is a hydrogen atom and the other is a carboxyl group, a lower alkylcarbonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonylalkylcarbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a morpholinocarbonyl group, a piperidin-1-ylcarbonyl group which may be substituted by a methyl group or a hydroxyl group in 4-position, an N-phenylcarbamoyl group or a group

represented by the formula $-CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$ or a lower alkyl group optionally substituted by R_{15}; R_{10}, R_{11} and R_{12} are independently a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4, R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group;

or R_{6a} and R_{6b} are both a lower alkyl group; Q is an aryl group optionally substituted by any 1 - 4 halogen atoms or an aryl lower alkenylene group optionally substituted by any 1 - 4 halogen atoms).

[Claim 2]

The compound or a salt thereof according to claim 1, wherein G_1 is N, G_2 and G_3 are both CH and Q is a naphthyl group optionally substituted by any 1 - 4 halogen atoms or a styryl group which may be similarly substituted.

[Claim 3]

The compound or a salt thereof according to claim 2, wherein one of R_{6a} and R_{6b} is a hydrogen atom and the other is 1) a group selected from among a carboxyl group, a lower

alkylcarbonyl group, a lower alkoxycarbonyl group and a lower alkoxycarbonylalkylcarbonyl group;

2) a group selected from among an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a morpholinocarbonyl group, a piperidin-1-ylcarbonyl group which may be substituted by a methyl group or a hydroxyl group in 4-position, an N-phenylcarbamoyl group or a group represented by the formula -$CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$ (wherein R_{10}, R_{11} and R_{12} are independently a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group); p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4, or

3) a lower alkyl group optionally substituted by R_{15}; R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group;

or R_{6a} and R_{6b} are both lower alkyl groups.

[Claim 4]

The compound or a salt thereof according to claim 3, wherein one of R_{6a} and R_{6b} is a hydrogen atom and the other is a

carboxyl group, a lower alkylcarbonyl group, a lower alkoxycarbonyl group or a lower alkoxycarbonylalkylcarbonyl group, or a lower alkyl group substituted by R_{15}; R_{15} is a hydroxyl group, a lower alkoxy group or a lower acyloxy group.

[Claim 5]

A compound selected from the following list or a salt thereof:

4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-hydroxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methoxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-acetoxymethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-[(E)-4-chlorostyrylsulfonyl]-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-carboxy-4-[(E)-4-chlorostyrylsulfonyl]-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-aminocarbonyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-aldoximyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-

2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethylaminocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methoxyaminocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinecarbonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-aminomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethylaminomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-acetamidomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methanesulfonylamidomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinemethyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(2-naphthylsulfonyl)-6-hydroxymethyl-1-[1-(4-pyridyl)piperidin-4-

ylmethyl]piperazin-2-one; 6-acetoxymethyl-4-(2-naphthylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; (R)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; and (S)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one.

[Claim 6]

A pharmaceutical composition containing at least one compound or a salt thereof according to any one of claims 1 - 5 as an active ingredient.

[Claim 7]

The pharmaceutical composition according to claim 6, which is an inhibitor of activated blood coagulation factor X.

[Claim 8]

The pharmaceutical composition according to claim 6, which is an anticoagulant.

[Claim 9]

The pharmaceutical composition according to claim 6, which is a preventive and/or a therapeutic of disease caused by thrombus or embolus.

[DETAILED DESCRIPTION OF THE INVENTION]

[0001]

[Technical Field of the Invention]

This invention relates to orally administrable aromatic compounds having cyclic amino groups or salts thereof that are useful as pharmaceuticals, particularly as an inhibitor of activated blood coagulation factor X (hereunder referred to as FXa), and which show potent anticoagulation action.

[0002]

[Prior Art]

With the recent shift to western life style and the increasing number of aged people, the incidence of thromboembolic diseases including ischemic heart diseases and many other cardiovascular lesions, in particular, myocardial infarction, cerebral thrombosis, pulmonary embolism and peripheral arteriovenous obstruction is increasing each year and the social importance of treating those diseases is ever increasing. In the treatment and prevention of these thrombotic cases, anticoagulation therapy as well as antiplatelet therapy and fibrinolytic therapy are important medical therapeutic methods. For the treatment and prevention of thrombosis, safety that permits long-term drug administration and the development of a positive and appropriate anticoagulant activity are essential.

[0003]

Heretofore, anticoagulants such as warfarin and heparin have been used in order to prevent and treat thrombosis due to hypercoagulability but, at the same time, many defects of them have been pointed out, including the risk of bleeding and interactions with other drugs. Warfarin is extensively used in the world as the sole peroral anticoagulant. However, due to its characteristics based on the mechanism of action, the concentration range for the development of efficacy is narrow and yet it takes long to develop efficacy and the half-life in blood is as long as 36 hours; what is more, for several reasons such as the great individual difference of effective dose, it is difficult to control the anticoagulability of warfarin (N. Eng. J. Med. 324 (26) 1865-1875, 1991) and frequent monitoring is necessary to prevent bleeding as a side effect; in addition, warfarin has many other side effects such as nausea, vomiting, diarrhea and alopecia; thus, warfarin is a drug that involves considerable difficulty in clinical use. On the other hand, heparin is extensively used in the world as an intravenously administrable anticoagulant. However, since it is a direct inhibitor of thrombin, heparin has a high risk of bleeding and needs as frequent monitoring as warfarin; what is more, due to its characteristics based on the mechanism of action, adequate coagulation inhibiting effect is not expected

at a lowered antithrombin III level; thus, heparin is a drug that involves considerable difficulty in clinical use. Under these circumstances, the advent of an improved anticoagulant has been desired that has none of the defects inherent in warfarin and heparin.

[0004]

The blood coagulation cascade is a chain reaction involving restricted protein decomposition that starts upon activation of an extringic or intringic coagulation cascade and, once activated, the reaction amplifies like an avalanche. Since the final stage of the blood coagulation cascade is thrombin-mediated conversion of fibrinogen to fibrin, efforts have recently been made to develop thrombin inhibitors; however, drugs that directly inhibit thrombin are known to increase the risk of bleeding. In addition, they have low bioavailability in oral administration and no commercial thrombin inhibitor has ever been proposed that can be administrated perorally.

[0005]

FXa which is located upstream of thrombin in the coagulation cascade is a key enzyme found at the point of convergence between the extringic and intringic coagulation cascades and one molecule of FXa is known to produce about 100

molecules of thrombin per minute. Hence, an FXa inhibitor can potentially inhibit the coagulation cascade more efficiently than a thrombin inhibitor (Thrombosis Research, Vol. 19, 339-349, 1980; Mebio, Vol. 14, No. 8, 1997).

[0006]

Compounds that exhibit FXa inhibiting actions have been disclosed in several patents, among which Japanese Patent Application Laid-Opened No. 208946/1993 and WO96/16940 disclose aromatic amidine derivatives, in particular, amidinonaphthyl derivatives, and WO97/38984 discloses cyclic urea compounds having an amidinophenyl group. However, these compounds are still in the process of development and none have been commercialized to date. In addition to low bioavailability, they have slight dissociations to be improved between the thrombin inhibiting action and the FXa inhibiting action and there is also a concern about the possible occurrence of side effects such as hypotension and dyspnea due to the amidino group.

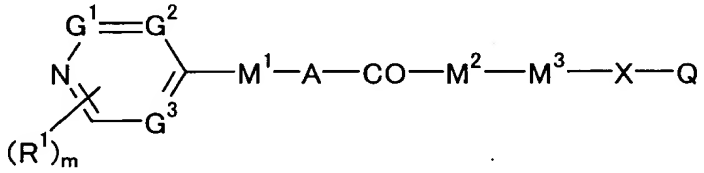
[0007]

Referring to the compounds it discloses, Japanese Patent Application Laid-Opened No. 208946/1993 teaches using them as an agent for preventing and treating infections with influenza

virus by means of their activity in inhibiting the growth of the influenza virus based on the FXa inhibiting action.

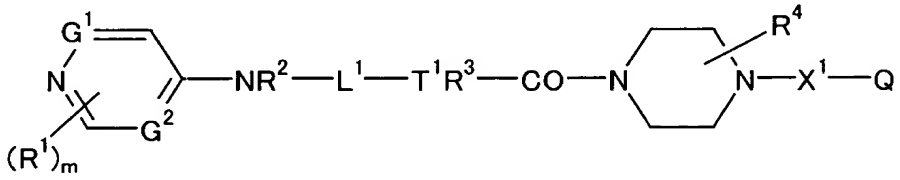
Compounds having an aminoheterocyclic group typified by 1-(4-pyridyl)piperidin-4-yl group can be used as an FXa inhibitor; for example, WO96/10022 discloses

[Chemical Formula 2]



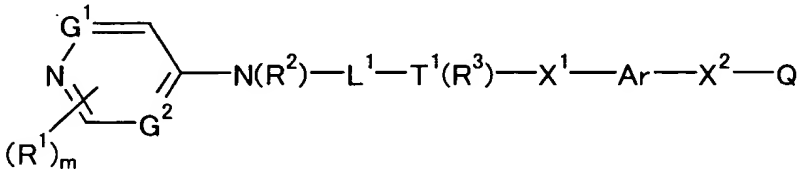
(the definitions of the substituents in the formula are omitted), WO97/29104 discloses

[Chemical Formula 3]



(the definitions of the substituents in the formula are omitted), and WO97/28129 discloses

[Chemical Formula 4]



(wherein ... Ar is phenylene or a single 5- or 6-membered aromatic heterocyclic ring containing up to three hetero atoms

selected from among a nitrogen atom, an oxygen atom and a sulfur atom, ...).

[0008]

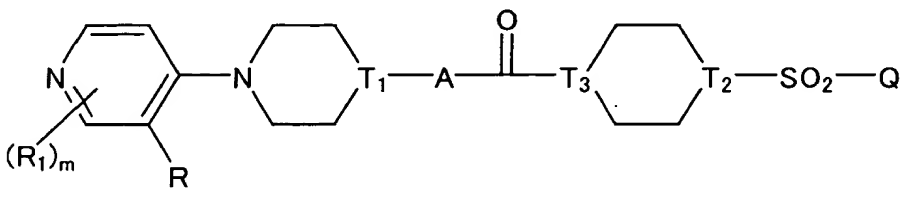
It has been reported that some of the compounds disclosed in those patents have the activity of inhibiting oxidosqualene cyclase (WO97/06802 and WO97/28128).

However, as of today, none of these compounds have been commercialized as pharmaceuticals. The five patents mentioned above claim extremely broad scope of compounds but the bridge group linking two rings comprising combinations of piperazine or piperidine rings requires the presence of a carbonyl group as an essential component and there are no derivatives in which the two rings are bridged by an alkylene group alone or they are directly linked by a single bond.

[0009]

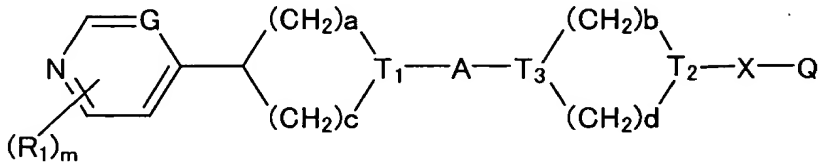
With respect to an oxidosqualene cyclase inhibitor, two patents have been published that disclose the following two structures. WO98/35956 discloses

[Chemical Formula 5]



(the definitions of the substituents in the formula are omitted) and WO98/35959 discloses

[Chemical Formula 6]



(the definitions of the substituents in the formula are omitted).

Like the compounds of other prior art techniques, the former compound requires the presence of a carbonyl group in the bride group as an essential component. The latter compound mainly has 4-(4-pyridyl)piperidin-1-yl group as the basic skeleton and because of this basic structural feature, it differs from the compounds of the present invention. According to the description, A is preferably C_{1-4} alkylenecarbonyl or carbonyl. The specification of neither patent suggests the FXa inhibiting activity.

[0010]

Compounds having an aminoheterocyclic group typified by 1-(4-pyridyl)piperidin-4-yl group can also be used as a platelet agglutination inhibitor and they have been disclosed in many patent applications including, for example, WO94/22834, WO94/22835, WO96/38416, EP718287, WO96/24581 and WO96/19223. However, intending to inhibit GPIIb/IIIa, the

compounds disclosed in these patents have a characteristic structure in that an aliphatic carboxyl group, an aliphatic alkoxycarbonyl group or the like is positioned in a terminal side chain of the molecule remote from the aminoheterocyclic ring. FXa inhibiting action has not been reported for these compounds.

[0011]

In the development of pharmaceutical products, the desired pharmacological activity is not the sole requirement but long-term safety is also needed. Another requirement is that strict criteria be met in various aspects including absorption, distribution, metabolism and excretion. To mention a few examples, drug interactions, desensitization or tolerance, gastrointestinal absorption upon oral administration, rate of transfer into the small intestine, absorption rate and the first pass effect, organ barrier, protein binding, induction of drug metabolizing enzymes, route of excretion and in vivo clearance, dose regimen (site of application, its method and object) and various other considerations need be satisfied but only a limited number of compounds have been found to meet these criteria.

Anticoagulants are not an exception and they are at all times required to satisfy the above-mentioned considerations

in the development of pharmaceuticals. In addition, an FXa inhibitor must avoid the aforementioned problem of side effects in oral administration of warfarin, as well as the risk of bleeding due to the thrombin inhibiting activity of heparin which can be administered only by intravenous injection.

[0012]

[Problems to be Solved by the Invention]

Under these circumstances, an anticoagulant drug is needed that has high safety, exhibits high efficacy and provides greater ease of use. To be more specific, an anticoagulant drug is pressingly needed that has solved at least one of the aforementioned problems by, for example, eliminating interactions with other drugs, reducing side effects such as the risk of bleeding or improving dose response and which is orally administrable to mammals including man, with the particular advantage of being very convenient to use in clinical settings.

[0013]

[Means to Solve the Problems]

With a view to meeting this demand, the present inventors made intensive studies to provide compounds having an enhanced FXa inhibiting action. As a result, they found that among the

aromatic compounds having cyclic amino groups, those of the formula (I) in which two rings comprising a piperidine ring and a piperazine ring are bridged together by a methylene group and in which the nitrogen atom on the piperazine ring is substituted with a group represented by the formulaeO_2-Q, had an outstanding FXa inhibiting action. The present invention has been accomplished on the basis of this finding.

[0014]

[Embodiments of the Invention]

On the pages that follow, we describe the present invention in detail. The present invention relates to aromatic compounds having cyclic amino groups as represented by the formula (I) to be set forth below or salts thereof.

To be specific, a first aspect of the present invention is to provide compounds represented by the formula (I) to be set forth below or pharmaceutically acceptable salts thereof.

[0015]

A second aspect of the present invention is to provide a pharmaceutical composition characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

A third aspect of the present invention is to provide a FXa inhibitor characterized by containing a compound

represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient. More particularly, the inhibitor is a FXa specific inhibitor, or an orally FXa administrable inhibitor, or an orally administrable FXa specific inhibitor.

[0016]

A fourth aspect of the present invention is to provide an anticoagulant characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

A fifth aspect of the present invention is to provide a preventive and/or a therapeutic agent for disease caused by thrombus or embolus that is characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

A sixth aspect of the present invention is to provide a preventive and/or a therapeutic agent for disease against which an anticoagulant is effective, characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

[0017]

A seventh aspect of the present invention is to provide a

preventive and/or a therapeutic agent for disease against which an FXa inhibitor is effective, characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

An eighth aspect of the present invention is to provide a preventive and/or a therapeutic agent for embolus that accompanies atrial fibrillation, heart valve replacement or valvular heart disease, characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient. Preferably, it relates to a preventive for the onset of cerebral embolism that accompanies these diseases.

A ninth aspect of the present invention is to provide a preventive and/or a therapeutic agent for transient cerebral ischemic attacks characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient. It particularly relates to a preventive agent for the recurrence of transient cerebral ischemic attacks.

[0018]

A tenth aspect of the present invention is to provide a preventive and/or a therapeutic agent for DIC characterized by

containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

An eleventh aspect of the present invention is to provide a preventive and/or a therapeutic agent for influenza viral infections characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

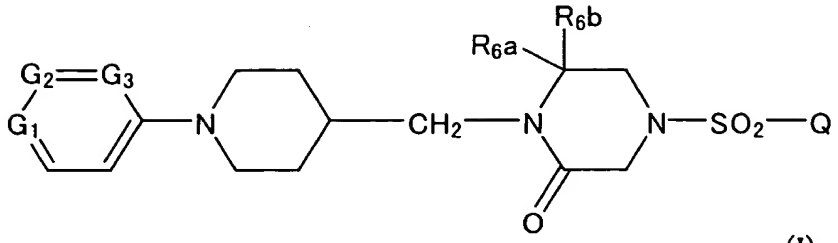
A twelfth aspect of the present invention is to provide a preventive and/or a therapeutic agent for deep venous thrombosis characterized by containing a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof as an active ingredient.

[0019]

The compounds of the present invention are aromatic compounds having cyclic amino groups as represented by the following formula (I) or pharmaceutically acceptable salts thereof:

[0020]

[Chemical Formula 7]



(I)

(wherein G_1, G_2 and G_3 are independently CH or N, provided that at least one of them is N; one of R_{6a} and R_{6b} is a hydrogen atom and the other is a carboxyl group, a lower alkylcarbonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonylalkylcarbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a morpholinocarbonyl group, a piperidin-1-ylcarbonyl group which may be substituted by a methyl group or a hydroxyl group in 4-position, an N-phenylcarbamoyl group or a group represented by the formula - $CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$ or a lower alkyl group optionally substituted by R_{15}; R_{10}, R_{11} and R_{12} are independently a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4, R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a

lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group; or R_{6a} and R_{6b} are both a lower alkyl group; Q is an aryl group optionally substituted by any 1 - 4 halogen atoms or an aryl lower alkenylene group which may be similarly substituted).

It should be noted that the compounds of the present invention are clearly different from the compounds described in connection with the prior art in that they have two rings comprising the combination of a piperazine ring and a piperidine ring, with no carbonyl group being present in the bridge group between the two rings, and that the molecule has no terminal alkyl side chain that is substituted by a carboxyl group, an alkoxycarbonyl group or the like.

[0021]

Further referring to the compounds of the present invention, those in which a piperazine ring and a piperidine ring are bridged by methylene, particularly one that is substituted by a pyridin-4-yl group, have not been synthesized to date since intermediates for them (compounds of the formula (III) to be set forth below) have been difficult to obtain in a consistent manner. Therefore, although a multitude of compounds were disclosed or contemplated in the aforementioned prior art patents, the compounds of the present invention were

not obtained or contemplated as the final compounds. As a result of many considerations on the reaction process and the intensive studies that followed, the present inventors captured the above-mentioned intermediates as reactive ones by the reaction methods to be described in the present invention and successfully produced the final compounds in high yield. It should be noted that those intermediates are also applicable to the synthesis of organic compounds other than the final compounds of the present invention.

[0022]

In the definitions of the groups in the structural formulae of the present invention,

the "halogen atom" is exemplified by a fluorine atom, a chlorine atom, a bromine atom and an iodine atom; a chlorine atom and a bromine atom are preferred;

the term "lower", unless otherwise noted, refers to a straight or branched carbon chain having 1 - 6 carbon atoms; therefore, the "lower alkyl group" may be exemplified by a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a pentyl group, an isopentyl group, a neopentyl group, a tert-pentyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 1,2-dimethylpropyl group, a hexyl

group, an isohexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1,2-trimethylpropyl group, a 1,2,2-trimethylpropyl group, a 1-ethyl-1-methylpropyl group and a 1-ethyl-2-methylpropyl group; among these, alkyl groups having 1 - 3 carbon atoms are preferred, and a methyl group and an ethyl group are particularly preferred;

[0023]

the "lower alkoxy group" may be exemplified by a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, an isobutoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy(amyloxy) group, an isopentyloxy group, a tert-pentyloxy group, a neopentyloxy group, a 2-methylbutoxy group, a 1,2-dimethylpropoxy group, a 1-ethylpropoxy group and a hexyloxy group; preferred lower alkoxy groups are those having 1 - 3 carbon atoms, and a methoxy group and an ethoxy group are particularly preferred;

[0024]

the "lower alkoxycarbonyl group" may be exemplified by a methoxycarbonyl group, an ethoxycarbonyl group, a

propoxycarbonyl group, an isopropoxycarbonyl group, a butoxycarbonyl group, an isobutoxycarbonyl group, a sec-butoxycarbonyl group, a tert-butoxycarbonyl group, a pentyloxycarbonyl group, an isopentyloxycarbonyl group, a neopentyloxycarbonyl group, a tert-pentyloxycarbonyl group, a hexyloxycarbonyl group and other groups that form an ester between a straight-chained or branched alcohol having 1 - 6 carbon atoms and a carboxyl group; preferred lower alkoxycarbonyl groups are those having 1 - 3 carbon atoms, and a methoxycarbonyl group and an ethoxycarbonyl group are given as examples;

[0025]

by the "mono- or di-substituted lower alkylamino group" is meant an amino group in which one or two hydrogen atoms are replaced by the above-defined "lower alkyl group"; specific examples include a methylamino group, an ethylamino group, a propylamino group, an isopropylamino group, a butylamino group, an isobutylamino group, a pentylamino group, an isopentylamino group, a hexylamino group and an isohexylamino group. The dialkylamino group may be of a symmetric type which is di-substituted by a straight-chained or branched alkyl group having 1 - 6 carbon atoms, as exemplified by a dimethylamino group, a diethylamino group, a dipropylamino

group, a diisopropylamino group, a dibutylamino group and a dipentylamino group, or it may be of a type that is asymmetrically substituted by a straight-chained or branched alkyl group having 1 - 6 carbon atoms, as exemplified by an ethylmethylamino group, a methylpropylamino group, an ethylpropylamino group, a butylmethylamino group, a butylethylamino group and a butylpropylamino group;

[0026]

the "cyclic amino group" may be a cyclic cycloalklylamino group that may have a branched chain of 2 - 6 carbon atoms, as exemplified by a pyrrolidinyl group, a piperidinyl group or a methylpiperidinyl group, or it may be a saturated cyclic amino group as exemplified by a morpholino group or a piperazinyl group;

these cyclic amino groups further include those which are substituted by a lower alkyl group or a hydroxyl group and a preferred example is a 4-hydroxy-1-piperidinyl group;

[0027]

the "lower alkanoylamino group" is a group in which the hydrogen atom in an amino group is substituted by the lower alkanoyl group and examples include a formylamino group, an acetylamino group, a propionylamino group, a butyrylamino group, an isobutyrylamino group, a valerylamino group, an

isovalerylamino group, a pivaloylamino group and a hexanoylamino group, with an acetylamino group, a propionylamino group and a butyrylamino group being preferred;

[0028]

the "aryl group", unless otherwise noted, is an aryl group in the form of a monocyclic or fused hydrocarbon ring having 6 - 14 carbon atoms and may specifically be exemplified by a phenyl group, a naphthyl group, a biphenylyl group and an anthryl group, with a phenyl group, a naphthyl group and a p-biphenylyl group being preferred;

the "aryl lower alkenylene group" is a group in which the above-defined aryl group is attached to a lower alkenylene group such as a vinylene group, a propenylene group or an isopropenylene group and a preferred example is a styryl group;

[0029]

the "optionally mono- or di-lower alkyl substituted carbamoyl group" may be exemplified by a carbamoyl group, an N-methylcarbamoyl group, an N-ethylcarbamoyl group, an N,N-dimethylcarbamoyl group, an N,N-diethylcarbamoyl group and an N-ethyl-N-methylcarbamoyl group;

[0030]

the "lower alkoxycarbonylalkylcarbamoyl group" is a group in which the above-defined "lower alkoxycarbonyl group" is substituted in the alkyl group of the above-defined "mono- or di-lower alkyl substituted carbamoyl group" and examples include a methoxycarbonylmethylcarbamoyl group, an ethoxycarbonylmethylcarbamoyl group and an ethoxycarbonylethylcarbamoyl group;

[0031]

the "lower acyloxy group" is a hydroxyl group substituted by the above-defined "lower alkylcarbonyl group" and examples include an acetyloxy group and an ethylcarbonyloxy group;

[0032]

the "lower alkylsufonylamino group" is a sulfonylamino group having the above-defined "lower alkyl group" and examples include a methanesulfonylamino group, an ethanesulfonylamino group and a propanesulfonylamino group;

[0033]

The following are the preferred definitions of the substituents in the compounds of the present invention.

As for G_1 - G_3 in the formula (I), preferred cases are as follows: G_1 is N and G_2 and G_3 are CH; G_2 is N and G_1 and G_3 are CH; G_3 is N and G_1 and G_2 are CH; G_1 and G_2 are N and G_3 is CH; G_1

and G_3 are N and G_2 is CH; a more preferred case is as follows: G_1 is N and G_2 and G_3 are CH.

[0034]

Preferably, one of R_{6a} and R_{6b} is a hydrogen atom and the other is a carboxyl group, a lower alkylcarbonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonylalkyl-carbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a morpholinocarbonyl group, a piperidin-1-ylcarbonyl group which may be substituted by a methyl group or a hydroxyl group in 4-position, an N-phenylcarbamoyl group or a group represented by the formula $-CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$ or a lower alkyl group optionally substituted by R_{15}; R_{10}, R_{11} and R_{12} are independently a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4, R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group

or an N-hydroxyimino group; or R_{6a} and R_{6b} are both lower alkyl groups;

more preferably,

either one of R_{6a} and R_{6b} is a hydrogen atom and the other is a carboxyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a carboxymethyl group, a methoxycarbonylmethyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonylalkylcarbonyl group or a lower alkyl group that may be substituted by R_{15}; R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group (aldoxime group); or R_{6a} and R_{6b} are both lower alkyl groups;

[0035]

the aryl group Q is an aryl group in the form of a monocylic or fused hydrocarbon ring having 6 - 14 carbon atoms and is preferably a phenyl group, a biphenyl group, a 1-naphthyl group or a 2-naphthyl group; a 2-naphthyl group is particularly preferred; the optionally substituted arylalkenyl group Q is preferably an optionally substituted styryl group;

a 6-halogen substituted-2-naphthyl group and a p-halogen substituted styryl group are more preferred;

[0036]

the halogen atoms by which these aryl groups may be substituted include a fluorine atom, a chlorine atom, a bromine atom and a sulfur atom. A chlorine atom and a bromine atom are preferred. The above groups are preferably mono- or di-substituted, and more preferably mono-substituted.

[0037]

The compounds of the present invention are those of the formula (I) or salts thereof. The following are specific examples of the compounds having the preferred combinations of substituents.

(1) Compounds of the formula (I) where at least G_1 is N are preferred.

More preferred are the compounds where G_2 and G_3 are CH or G_3 is N and G_2 is CH in the combination of G_2 and G_3;

one of R_{6a} and R_{6b} is a hydrogen atom and the other is a carboxyl group, a lower alkylcarbonyl group, a lower alkoxycarbonyl group, a lower alkoxycarbonylalkylcarbonyl group, an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl

group, a morpholinocarbonyl group, a piperidin-1-ylcarbonyl group which may be substituted by a methyl group or a hydroxyl group in 4-position, an N-phenylcarbamoyl group or a group represented by the formula $-CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$ or a lower alkyl group optionally substituted by R_{15}; R_{10}, R_{11} and R_{12} are independently a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group; or R_{6a} and R_{6b} are both a lower alkyl group;

Q is a phenyl group, a biphenyl group, a 1-naphthyl group, a 2-naphthyl group or a styryl group, provided that these groups may be substituted by any 1 - 4 halogen atoms.

[0038]

Further preferred are the following compounds or salts thereof: G_1 is N and G_2 and G_3 are CH; one of R_{6a} and R_{6b} is a hydrogen atom and the other is

1) a group selected from among a carboxyl group, a lower alkylcarbonyl group, a lower alkoxycarbonyl group and a lower alkoxycarbonylalkylcarbonyl group;

2) a group selected from among an optionally mono- or di-lower alkyl substituted carbamoyl group, a lower alkoxycarbamoyl group, a lower alkoxycarbonylalkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a morpholinocarbonyl group, a piperidin-1-ylcarbonyl group which may be substituted by a methyl group or a hydroxyl group in 4-position, an N-phenylcarbamoyl group or a group represented by the formula -$CONH(CH_2)_pS(O)_qR_{10}$ or $CONH(CH_2)_rNR_{11}R_{12}$ (wherein R_{10}, R_{11} and R_{12} are independently a hydrogen atom, a lower alkyl group, a phenyl group or a lower alkylphenyl group; p is an integer of 0 - 4, q is an integer of 0 - 2, and r is an integer of 1 - 4), or 3) a lower alkyl group optionally substituted by R_{15}; R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group (aldoxime group);

or R_{6a} and R_{6b} are both lower alkyl groups;

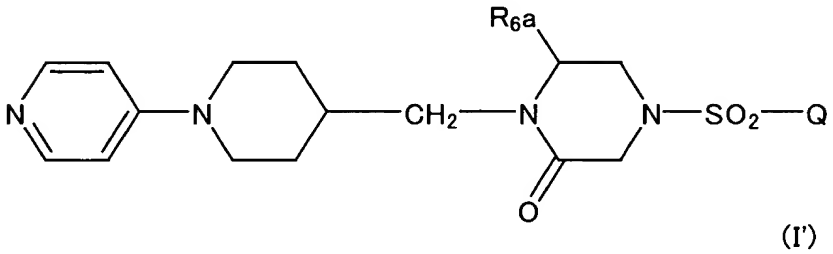
Q is a phenyl group, a 1-naphthyl group, a 2-naphthyl group, a biphenylyl group or a styryl group, provided that these aromatic rings are either unsubstituted or mono-, di- or tri-substituted by any substituent selected from among a

fluorine atom, a chlorine atom, a bromine atom and an iodine atom, particularly a chlorine atom and a bromine atom, Q being preferably a 6-halogeno-2-naphthyl group or a p-halogenostyryl group.

[0039]

Particularly preferred are the compounds represented by the formula (I') or salts thereof:

[Chemical Formula 8]



(I')

(wherein R_{6a} and Q have the same meanings as defined for the substituent R_{6a} and Q in the formula (I); more preferably, R_{6a} is a carboxyl group, a lower alkoxycarbonyl group or a lower alkyl group optionally substituted by R_{15}; R_{15} is a carboxyl group, a lower alkoxycarbonyl group, a hydroxyl group, a lower alkoxy group, a lower acyloxy group, an amino group, a mono- or di-substituted lower alkylamino group, a lower alkanoylamino group, a lower alkylsulfonylamino group, a cyclic amino group or an N-hydroxyimino group (aldoxime group); Q is a phenyl group, a 1-naphthyl group, 2-naphthyl group, a biphenylyl group or a styryl group, provided that

these aromatic rings are either unsubstituted or mono-, di- or tri-substituted by any substituent selected from among a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, particularly a chlorine atom and a bromine atom, Q being more preferably a 6-halogeno-2-naphthyl group or a p-halogenostyryl group).

[0040]

Further, preferred examples of the compounds and salts thereof according to the present invention are specifically listed below:

4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-hydroxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methoxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-acetoxymethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-[(E)-4-chlorostyrylsulfonyl]-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-carboxy-4-[(E)-4-chlorostyrylsulfonyl]-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-aminocarbonyl-

4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-aldoximyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethylaminocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methoxyaminocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinecarbonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-aminomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethylaminomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-acetamidomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methanesulfonylamidomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinemethyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(6-

chloronaphthalen-2-ylsulfonyl)-6-dimethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 4-(2-naphthylsulfonyl)-6-hydroxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; 6-acetoxymethyl-4-(2-naphthylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; (R)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; and (S)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one; and methanesulfonates of the respective compounds.

[0041]

In the compounds of the present invention, the carbon atom to which the substituents R_{6a} and R_{6b} are attached is sometimes asymmetric depending on the type of the substitutents. Therefore, the compounds of the invention include various stereoisomers such as geometrical isomers, tautomers and optical isomers, either in admixture or isolated form. To isolate and purify these stereoisomers, the person skilled in the art may employ any ordinary techniques including optical resolution by preferential crystallization or column chromatography or asymmetric synthesis.

[0042]

The compounds (I) of the present invention occasionally form acid addition salts. Depending on the type of substituents, they also form salts with bases. While there are no particular limitations on the salts that can be formed as long as they are pharmaceutically acceptable, specific examples include: acid addition salts as with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric acid, organocarboxylic acids such as acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, formic acid, malic acid, tartaric acid, citric acid and mandelic acid, organosulfonic acids such as methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid and 2-hydroxyethanesulfonic acid, and acidic amino acids such as aspartic acid and glutamic acid; salts with alkali metals or alkaline earth metals (e.g. sodium, potassium, magnesium, calcium and aluminum), and organic bases such as methylamine, ethylamine, ethanolamine, pyridine, lysine, arginine and ornithine; and ammonium salts.

[0043]

Further, the present invention encompasses hydrates of the compounds (I), pharmaceutically feasible various solvates of the compounds, their polymorphs and the like. Needless to

say, the present invention is not limited to the compounds described in the Examples to be set forth later but encompasses all aromatic compounds having cyclic amino groups as represented by the formula (I), and all pharmaceutically acceptable salts thereof.

[0044]

On the pages that follow, the production methods are described in detail.

The compounds of the present invention which are represented by the formula (I) can be produced by the methods described below. In the following Production Method 1, Production Method 2 and the explanation, the definitions of R_{6a}, R_{6b}, G_1, G_2, G_3 and Q in the formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) are the same as the former definitions described in the formula (I). The compounds of the present invention which are represented by the formula (I) and salts thereof can be synthesized by Production Method 1, starting from compounds represented by the formulae (II) and (XI) or salts thereof which can be readily prepared from documented or commercial compounds.

[0045]

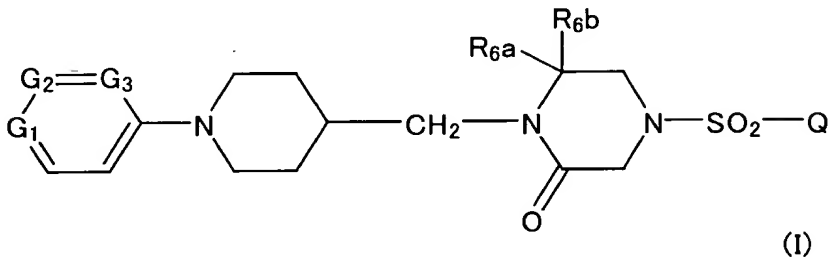
On the pages that follow, the production methods are described in detail.

<Production Method 1>

The method of producing the compounds represented by the formula (I) is described below.

Compounds represented by the formula (I):

[Chemical Formula 9]



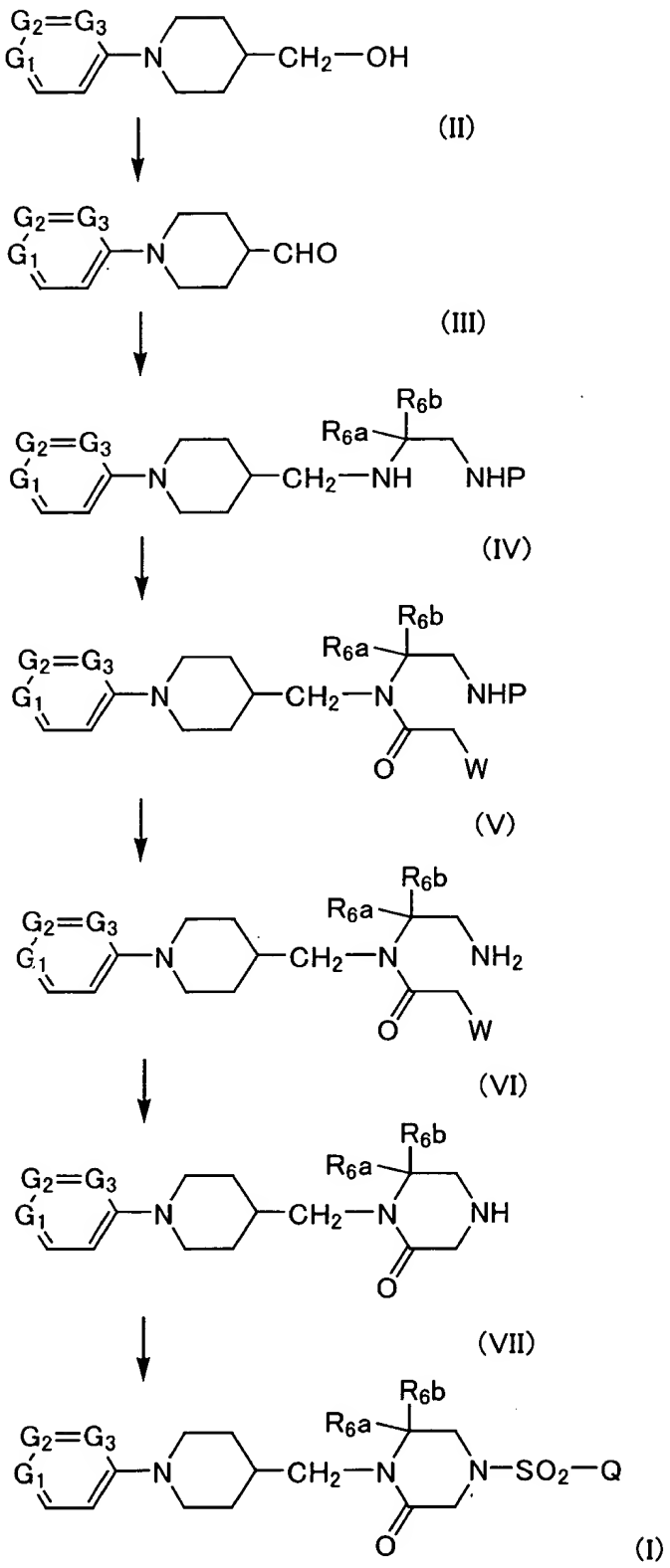
(I)

(wherein R_{6a}, R_{6b}, G_1, G_2, G_3 and Q have the same meanings as defined above) are produced by the following method as shown in Production Method 1.

[0046]

[Chemical Formula 10]

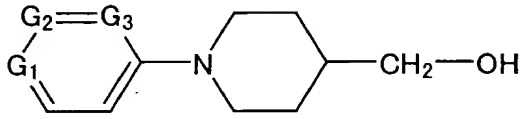
Production Method 1


G2=G3
G1
N
CH2—OH
(II)
CHO
(III)
R6b
R6a
CH2—NH
NHP
(IV)
O
W
(V)
NH2
(VI)
NH
(VII)
N—SO2—Q
(I)

[0047]

A compound of the formula (II) which can be readily derived from a commercial product or a salt thereof:

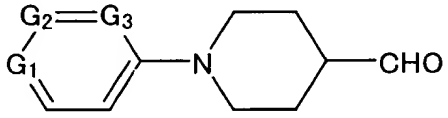
[Chemical Formula 11]



(II)

(wherein G_1, G_2 and G_3 have the same meanings as defined above) is subjected to an oxidation reaction to produce an aldehyde compound represented by the formula:

[Chemical Formula 12]



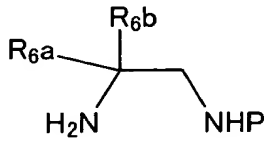
(III)

(wherein G_1, G_2 and G_3 have the same meanings as defined above). While the production method is described below in detail, it should be understood that the present invention is in no way limited to this method. The compound of the formula (II) is subjected to an oxidation reaction such as the Swern oxidation (dimethyl sulfoxide (DMSO)/oxalyl chloride), oxidation with tetrapropylammonium perruthenate (TPAP)/N-

methylmorpholine-N-oxide, the Corey-Kim oxidation (N-chlorosuccinimide (NCS)-dimethyl sulfide (DMS) complex), oxidation with pyridinium dichromate (PDC), oxidation with pyridinium chlorochromate (PCC) or the Jones oxidation ($Na_2Cr_2O_7$/Cr(VI)/sulfuric acid), preferably the Swern oxidation using DMSO/oxalyl chloride, in a halogenated hydrocarbon solvent typified by chloroform, methylene chloride and dichloroethane, preferably methylene chloride, at between -78°C and -60°C, preferably at between -78°C and -65°C, for a sufficient time to proceed the reaction to an adequate extent, specifically for 15 minutes to 1 hour, thereby producing a compound of the formula (III). Then, the compound of the formula (III) and a compound represented by the formula (VIII):

[0048]

[Chemical Formula 13]



(VIII)

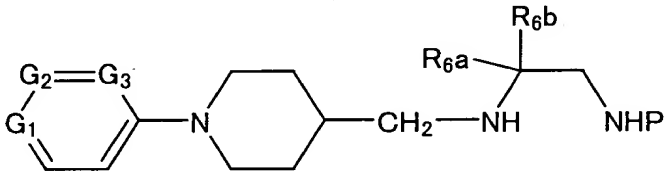
(wherein R_{6a} - R_{6b} have the same meanings as defined above; P is an amino protecting group such as a carbamate typified by t-butoxycarbonyl and benzyloxycarbonyl, an acyl typified by formyl, acetyl and benzoyl, or an alkyl typified by benzyl, allyl, trityl and methoxymetyl) are subjected to a reductive

amination reaction using a reducing agent such as sodium triacetoxyborohydride, sodium borohydride, lithium borohydride, diisobutylaluminum hydride or sodium cyanoborohydride, within a halogenated hydrocarbon solvent typified by chloroform, methylene chloride and dichlroethane, preferably methylene chloride, in the presence or absence of acetic acid, preferably in its presence, under an argon atmosphere. The reaction is performed at between -78°C and room temperature, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 3 - 12 hours,

[0049]

thereby producing a compound of the formula (IV):

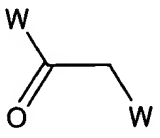
[Chemical Formula 14]



(IV)

Then, the compound of the formula (IV) and a reactive halogen derivative of the formula (IX):

[Chemical Formula 15]

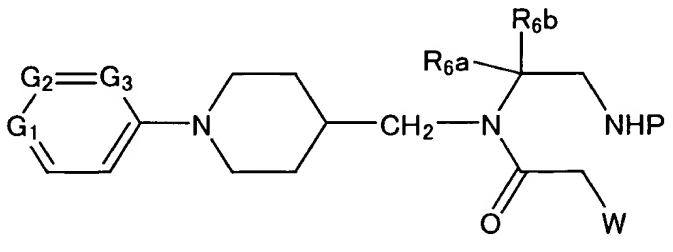


(IX)

(wherein W is a halogen atom) are subjected to a reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or DMF, a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether and tetrahydrofuran (THF), preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, thereby producing a compound of the formula (V):

[0050]

[Chemical Formula 16]



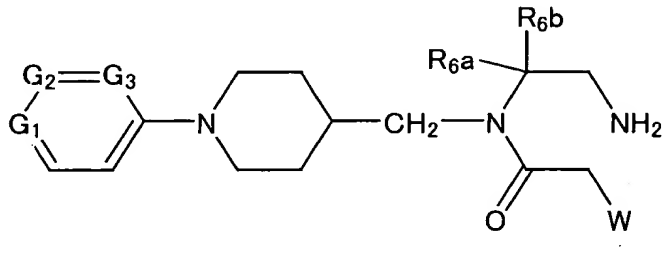
(V)

(wherein R_{6a}, R_{6b}, G_1, G_2, G_3, P and W have the same meanings as defined above). Then, the compound of the formula (V) is subjected to a deprotective reaction in the presence or

absence of anisole, preferably in its presence, using an acid such as trifluoroacetic acid, hydrochloric acid, sulfuric acid, p-toluenesulfonic acid or methanesulfonic acid, preferably trifluoroacetic acid, under an argon atmosphere at a temperature between under cooling with ice and room temperature, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 3 - 12 hours, thereby producing a compound of the formula (VI) (wherein R_{6a}, R_{6b}, G_1, G_2, G_3, P and W have the same meanings as defined above) or a salt thereof:

[0051]

[Chemical Formula 17]



(VI)

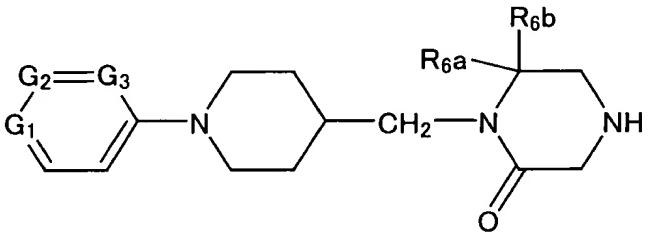
[0052]

Next, the reactive halogen derivative of the formula (VI) is subjected to a reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or

dimethylformamide (DMF), a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether and THF, preferably DMF, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, thereby producing a compound of the formula (VII) or a salt thereof:

[0053]

[Chemical Formula 18]



(VII)

(wherein R_{6a}, R_{6b}, G_1, G_2 and G_3 have the same meanings as defined above). Next, the compound of the formula (VII) or a salt thereof and a reactive halogen derivative of the formula (X):

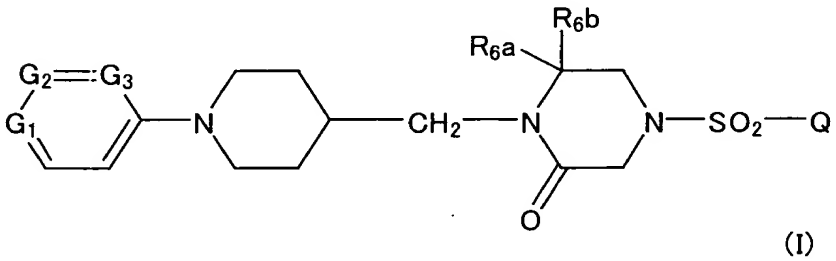
$$W\text{-}SO_2\text{-}Q \qquad (X)$$

(wherein W is a halogen atom and Q have the same meaning as defined above) are subjected to a reaction using an inorganic base such as potassium carbonate, cesium carbonate, calcium carbonate or sodium hydride or an organic base such as

triethylamine, pyridine or N,N-dialkylaniline, preferably triethylamine, within a polar solvent such as acetonitrile or DMF, a halogenated hydrocarbon solvent typified by chloroform and methylene chloride or an ether-based solvent typified by ether and tetrahydrofuran (THF), preferably methylene chloride, under an argon atmosphere at a temperature between room temperature and boiling point of the solvent used, preferably at room temperature, for a sufficient time to proceed the reaction to an adequate extent, specifically for 1 - 12 hours, thereby producing a compound of the formula (I) or a salt thereof:

[0054]

[Chemical Formula 19]



(I)

(wherein R_{6a}, R_{6b}, G_1, G_2, G_3 and Q have the same meanings as defined above).

[0055]

If some of the substituents in the compounds to be synthesized in the above-described Production Method 1 are reactive groups such as a hydroxyl group, an amino group, a

carboxyl group and a thiol group, these groups may be protected as appropriate in each reaction step, with the protective groups being removed at suitable stages. Protective groups may be introduced and removed as appropriate for the types of the groups to be protected and the protective groups used; reference may be had to the Review section of "Protective Groups in Organic Synthesis", 2nd Edition, 1991.

[0056]

We now describe the therapeutics, preventives and pharmaceutical compositions of the present invention. The pharmaceutical compositions of the present invention may contain at least one compound of the general formula (I) (as already defined above) as an active ingredient and they may also contain a pharmaceutically acceptable carrier. The preferred examples of the compounds of the general formula (I) have been described above.

The compounds of the present invention possess a potent FXa inhibitory activity. Hence, the compositions of the present invention are a potent FXa inhibitor, more particularly a specific FXa inhibitor that does not inhibit other enzymes. The compositions are also an orally administrable FXa inhibitor, as well as an orally administrable FXa specific inhibitor. While there are many

serine proteases, the activity of FXa is specifically inhibited by the compounds of the present invention and potently. They do not inhibit trypsin or chymotrypsin at all, nor do they inhibit thrombin which is another serine protease in the blood coagulation cascade. Hence, the compounds of the present invention solve the aforementioned problems with the conventional thrombin inhibitors, for example, the tendency to cause bleeding. As further advantages, the compounds of the present invention can be rapidly absorbed by the digestive tract after oral administration, their activity is not attenuated upon absorption, and they exhibit satisfactory characteristics in such aspects as absorption, distribution, metabolism and excretion. They therefore have high value of use as an oral drug.

[0057]

The compositions containing the compounds of the present invention can be used as preventives and/or therapeutics of diseases for which the FXa inhibitor is indicated. The compositions containing the compounds of the present invention can also be used as an anticoagulant, and as preventives and/or therapeutics of diseases for which the anticoagulant is indicated.

[0058]

In short, these drugs are effective in the prevention and/or treatment of diseases caused by thrombus or embolus. To mention specific examples of such diseases, they include: diseases from ischemic cerebrovascular disorders such as cerebral thrombosis, cerebral infarction, cerebral embolism, transient cerebral ischemic attacks (TIA) and cerebrovascular contractions after subarachnoid hemorrhage; diseases associated with ischemic heart diseases such as acute or chronic myocardial infarction, unstable angina pectoris and coronary thrombolysis; diseases from pulmonary infarction, pulmonary embolism and pulmonary angiopathy; and diseases from various cases of angiopathy including peripheral arterial obstruction, deep venous thrombosis, disseminated intravascular coagulation (DIC), thrombosis after artificial blood vessel or heart valve replacement, reocclusion and restenosis following coronary artery bypass surgery, reocclusion and restenosis on or after PTCA, and thrombosis on extracorporeal circulation of blood. The drugs find particular use in the prevention of embolism, preferably the onset of cerebral embolism, that accompanies atrial fibrillation, heart valve replacement or valvular heart disease, the prevention of transient cerebral ischemic

attacks, especially their recurrence, and in the prevention and treatment of deep venous thrombosis or DIC.

[0059]

If the drugs of the present invention are to be used as pharmaceuticals, administering them for the purpose of preventing the above-mentioned diseases is recommended and particularly important. The drugs of the present invention are not direct acting thrombolytic agents nor are they direct platelet agglutination inhibiting agents. Hence, they are preferably administered for preventive purposes to patients predisposed to thrombus formation or patients having the risk factor of thrombosis and embolism. In particular, patients who have atrial fibrillation, patients who underwent heart valve replacement and patients suffering from valvular heart disease have the high risk of thrombus formation in the lesions or the area of transplantation, which often triggers the development of cerebral infarction and the occurrence of fatal attacks is by no means rare. The drugs of the present invention are expected to prove extremely useful in preventing the induced thrombus or embolus formation in such patients, most preferably for preventing the onset of cerebral infarction.

Therapy on the above-mentioned conditions is performed over a prolonged period. The drugs of the present invention can be administered perorally, have less side effects such as bleeding, need no frequent monitoring and hence can be used safely for a prolonged time.

[0060]

In other words, the drugs of the present invention are preventives and/or therapeutics of embolus that accompanies atrial fibrillation, heart valve replacement or valvular heart disease. Preferably, they are preventives of the onset of cerebral embolism that accompanies these events. They are also preventives and/or therapeutics of transient cerebral ischemic attacks. In particular, they are preventives of the recurrence of the disease. They are also preventives and/or therapeutics of deep venous thrombosis or DIC.

Depending on the substituent R_{6a} or R_{6b}, some of the compounds of the present invention will easily undergo metabolism during drug absorption and distribution. Some of the resulting metabolites are also included in the formula (I) of the compounds of the present invention and possess potent FXa inhibitory activity, thus giving very interesting findings from pharmacological/pharmacokinetic viewpoints.

[0061]

The compositions containing the compounds of the present invention as an active ingredient are also effective as veterinary drugs and have high value of use. They are also useful in the measurement of various functional parameters in blood coagulation or as reagents in laboratories.

Since the compounds of the present invention have FXa inhibitory action, the compositions containing them can also be used as a preventive or therapeutic of the infection with influenza virus due to their activity in inhibiting the growth of the virus.

[0062]

Next, the outstanding FXa inhibitory activity of the compounds of the present invention can be verified by the following tests.

1) Measurement of Enzyme Inhibitory Action

a) Measuring human FXa inhibitory action

In vitro FXa inhibitory activity is measured according to the method of Kettner et al., J. Biol. Chem., 1990, 265, 18289-18297. That is, human FXa (Enzyme Research Laboratories, Inc., 0.019 U/ml) is mixed with a test compound diluted with dimethyl sulfoxide (DMSO) at various concentrations and a synthetic substrate S-2222 (Chromogenix AB, 0.4 mM) and incubated in a Tris-HCl buffer (pH 7.5) at 37

°C. The absorbance at 405 nm is measured continuously. To calculate the FXa inhibitory activity of the test compound, the initial reaction velocity is compared with the value for a control containing no test compound. The FXa inhibitory activity of a test compound is usually expressed as IC_{50}.

[0063]

The compounds of the present invention were measured for their FXa inhibitory activity by the above-described method and they had potencies between 0.1 nM and 1μM in terms of IC_{50}. The data for specific examples are shown in Table 1. The control compound in the assay system was 1-((E)-4-chlorostyrylsulfonyl)-4-[1-(4-pyridyl)piperidin-4-ylcarbonyl]piperazine (the compound synthesized in Example 39-2b of WO96/10022) and it had an IC_{50} of 0.15 μM.

[0064]

TABLE 1

Example No. of Compound	IC50 (μM)
Example 1	0.019
Example 2	0.0074
Example 8	0.017
Example 9	0.013
Example 14	0.012
Example 16	0.0085
Example 17	0.0070
Example 22	0.016
Example 23	0.070
Control	0.15

The compounds synthesized in the Examples of the present invention had potent inhibitory activities at least equal to that of the control compound.

[0065]

2) Measurement of Anticoagulation Activity (*in vitro*)

Thromboplastin time (PT) is measured in the presence of test compounds diluted at various concentrations. That is, a test compound diluted with DMSO at various concentrations is mixed with rat plasma and incubated at 37°C for 3 minutes. Then, a thromboplastin reagent is added and the coagulation time is measured. The anticoagulation activity of the test compound is indicated in terms of the concentration required to double the coagulation time for the case where no test

compound is added. In the actual test, the compounds of the present invention were found to be effective in extending the PT. The effectiveness of selected compounds of the present invention is shown in Table 2.

[0066]

TABLE 2

Compound of Example	PT Doubling Concentration (μM)
Example 1	2.8
Example 2	2.7

[0067]

3) Characteristics of Anticoagulation Activity (*ex vivo*)

a) *Ex vivo* anticoagulant studies in rats (i.v.)

Male Wistar rats (200 - 300 g; SLC, Inc.) that have been starved for more than 12 hours are administered through a femoral vein with a single dose of a drug (3 - 30 mg/kg) dissolved in physiological saline (or 10% DMSO solution) and blood is collected at given time intervals in 1/10th volume of 3.8% sodium citrate and centrifuged at 3000 rpm for 10 minutes to separate plasma, which is used in the following measurement of PT.

[0068]

A 50-μl portion of the above plasma is incubated at 37°C for 3 minutes and a thromboplastin solution (100 μl) is added

to start coagulation. The coagulation time is measured. In the actual test, the intravenously administered compounds of the present invention were found to be effective in extending the PT on account of enzyme inhibition.

[0069]

b) *Ex vivo* anticoagulant studies in rats (p.o.)

The above test a) was repeated, except that the administration of a single dose through a femoral vein was replaced by forced peroral administration via an oral probe. At given time intervals, blood was collected in 1/10th volume of 3.8% sodium citrate. As in the above test a), PT was measured.

In this test, the compounds of the present invention were found to be effective in extending the coagulation time upon oral administration of 10 - 100 mg/kg.

[0070]

In none of the *ex vivo* tests with rats was found any safety problem.

All that is required for the pharmaceutical compositions of the present invention is that they contain at least one of the compounds of the general formula (I) (as already defined above) or salts thereof as an active ingredient. They may also contain any pharmaceutically acceptable carriers. The

preferred examples of the compounds of the general formula (I) have already been mentioned.

[0071]

As described above, the compounds of the present invention show a potent FXa inhibitory activity and they have high specificity since they do not inhibit trypsin, chymotrypsin or thrombin. They exhibit antithrombotic action in rats if they are administered perorally at a dose of 0.3 - 3 mg/kg or administrated intravenously at a dose of 0.1 - 1 mg/kg. On the other hand, the compounds of the present invention in no way extend the bleeding time of rats even if they are administered perorally at a dose of 3 mg/kg or administrated intravenously at a dose of 1 mg/kg. Therefore, unlike the known anticoagulants such as heparin and warfarin, the compounds of the present invention exhibit the intended anticoagulation action without the risk of showing bleeding tendency. As a further advantage, the compounds of the present invention have good absorbability upon oral administration, their action lasts for a reasonable time and high safety is assured.

[0072]

To prevent or treat the various diseases mentioned hereinabove, the compounds of the present invention may be

administrated either individually or in combination with other pharmacologically active ingredients. Exemplary pharmacologically active ingredients include: known hemolytic agents [e.g. tissue plasminogen activator (tPA) and its derivatives (inclusive of modified products and derivatives of the so-called "second generation"), urokinase and streptokinase]; known anticoagulants (e.g. warfarin, heparin and thrombomodulin); known platelet agglutination inhibitors (e.g. aspirin, thromboxane antagonist, thromboxane synthesis inhibitor and GPIIb/IIIa inhibitor); known therapeutics of hyperlipidemia (e.g. clofibrate and related drugs, HMG-CoA inhibitor and EPA-E); and known antihypertensives (e.g. nifedipine and diltiazem). The term "combination" as used herein covers not only the administration of a combination drug containing both the compound of the present invention and another pharmacologically active ingredient but also the case where the two are in separate dosage forms and administered either at a time or at different times. The mode of administration is in no way limited as long as the compound of the present invention and another pharmacologically active ingredient exist simultaneously in the patient's blood.

[0073]

A pharmaceutical composition containing one or more of the compounds of the present invention and pharmaceutically acceptable salts thereof as an active ingredient may be formulated as capsules, pills, tablets, granules, subtilized granules and powders, drugs for internal application such as suspensions, emulsions, limonades, elixirs and syrups, as well as injections, nasal inhalants, suppositories, ointments and plasters using common pharmaceutical carriers, vehicles and other additives and thereafter applied to man and other animals either perorally or parenterally.

[0074]

The clinical dose at which the compounds of the present invention are to be administered to humans is determined as appropriate in consideration of various factors such as the symptoms of the patient to be treated, his or her body weight, age and sex; the usual daily dose for an adult ranges from 0.1 mg to 1000 mg, preferably from 1 mg to 300 mg (for oral administration), and from 0.01 mg to 300 mg, preferably from 0.1 mg to 100 mg (for parenteral administration), which is administrated either at a time or in divided portions. The dose is variable under actual conditions and smaller doses may sometimes suffice.

[0075]

The solid compositions to be administered perorally according to the present invention may be formulated as capsules, pills, tablets, powders, granules, etc. In these solid compositions, one or more active ingredients are combined with at least one inert carrier. Specific examples of inert carriers include vehicles (e.g. lactose, sucrose, mannitol, glucose, hyroxypropyl cellulose, microcrystalline cellulose and metasilicates), binders (e.g. crystalline cellulose, saccharides, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone and macrogol), lubricants (e.g. magnesium stearate, calcium stearate and talc), disintegrators (e.g. corn starch, carboxymethyl cellulose and cellulosic calcium glycolate), stabilizers (e.g. sugar alcohols and saccharides such as lactose), solubilizers or solvent promoters (e.g. cholesterol, triethanolamine, glutamic acid and aspartic acid), coloring agents, flavoring agents, antiseptics, isotonization agents, dispersing agents, antioxidants (e.g. ascorbic acid and butyl hydroxyanisole), buffers, and preservatives (e.g. paraben and benzyl alcohol). If necessary, tablets, pills, granules and the like may have gastric or enteric film coatings formed of sucrose, gelatin, hydroxyproopylmethyl cellulose phthalate, etc.

[0076]

Injections for parenteral administration include sterilized aqueous or non-aqueous solutions, suspensions and emulsions. Carriers for aqueous solutions and suspensions include, for example, distilled water for injection and physiological saline. Carriers for non-aqueous solutions and suspensions include, for example, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, alcohols such as ethyl alcohol, and polysorbate 80™. These compositions may further contain the additives exemplified above, for example, isotonization agents, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizers, solubilizers and solvent promoters. These compositions are sterilized by suitable techniques such as passage through a membrane filter, incorporation of sterilizers and irradiation with uv light. Sterile solid compositions may also be prepared and formulated as an injection that is dissolved, emulsified or suspended just prior to use. If the compounds of the present invention have low solubility, they may be subjected to a solubilizing treatment. Several solubilizing methods are known to be applicable to pharmaceutical preparations and they include the addition of surfactants (e.g. polyoxyethylene hydrogenated

castor oils, higher aliphatic acid esters of polyoxyethylene sorbitan and aliphatic acid esters of sucrose), and the formation of solid dispersions from the drug and solubilizers such as high-molecular weight compounds (e.g. water-soluble polymers such as polyethylene glycol (PEG), hydroxypropylmethyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP), and enteric polymers such as hydroxypropylmethyl cellulose phthalate (HPMCP) and methyl methacrylate-methacrylic acid copolymer (Eudragit L, S™; Rohm and Haas). If necessary, inclusion compounds may be formed using α-, β- or γ-cyclodextrin or hydroxypropyl cyclodextrin. These solubilizing methods may be modified as appropriate for the intended drug by having reference to literature such as "Yakugaku Monogurafu No. 1, Seibutsukagaku Riyono (Series of Monographs on Pharmacy, No. 1, Biochemical Availability)", Koji Nagai et al., Soft Science, 78-82 (1988) and "Saikin no Seizaigijutsu to Sono Oyo (Recent Advances in Pharmaceutical Formulation Technology and Its Applications)", Isamu Utsumi et al., Iyaku Journal, 157-159 (1983). Among the methods mentioned above, the formation of a solid dispersion from the drug and a solubilizer to enhance its solubility is recommended (Japanese Patent Application Laid-Opened No. 49314/1981 and FR 2460667).

[0077]

Pharmaceutical Preparations

The following are representative examples of the pharmaceutical compositions of the present invention. In the description, Compound M means the compound of the present invention which is represented by the formula (I) or a pharmaceutically acceptable salt thereof; specifically, it is any one of the compounds synthesized in the Examples that follow.

(a) Capsule (50 mg)

Compound M	100 g
Lactose	398.5 g
Magnesium stearate	1.5 g

Weighed amounts of the above ingredients were mixed uniformly and the resulting powder mixture was filled in 250-mg portions into hard capsules of JP No. 1.

[0078]

(b) Tablet (1 mg)

Compound M	1.0 g
Lactose	92.2 g
Carboxymethylcellulose sodium	5.0 g
Corn starch paste (5% W/V paste)	0.8 g
Magnesium stearate	1.0 g

Weighed amounts of the above ingredients were compressed into tablets in the usual manner, each weighing 100 mg.

[0079]

(c) Tablet (10 mg)

Compound M	10 g
Lactose	160 g
Croscarmellose sodium	4.0 g
Corn starch	20.7 g
Polyvinyl pyrrolidone	2.3 g
Magnesium stearate	3 g

Weighed amounts of the above ingredients were compressed into tablets in the usual manner, each weighing 200 mg. The tablets were then enteric-coated with cellulose acetate phthalate.

[0080]

(d) Tablet (100 mg)

Compound M	100 g
Lactose	181.5 g
Croscarmellose sodium	12 g
Corn starch (5% W/V paste)	3.5 g
Magnesium stearate	3 g

Weighed amounts of the above ingredients were compressed into tablets in the usual manner, each weighing 300 mg.

[0081]

(e) Injection (0.1 mg/ml)

Compound M	0.1 % W/V
Sodium phosphate buffered solution	2.3 % W/V
Citric acid	0.4%
Macrogol 400	3.5%
Water for injection	q.s. to make 100%

The above ingredients were mixed into solution and 1-ml portions of the solution were filled into injection ampules to make injections.

[0082]

(f) Injection (1.0 mg/ml)

Compound M	1.0% W/V
Sodium phosphate buffered solution	3.6% W/V
1 M Sodium hydroxide solution	15% W/V
Water for injection	q.s. to make 100%

The above ingredients were mixed into solution and 1-ml portions of the solution were filled into injection ampules to make injections.

[0083]

[Examples]

The following examples are provided for the purpose of further illustrating the present invention but are in no way to be taken as limiting.

Nuclear magnetic resonance (NMR) spectra were taken with JEOL JNM-EX270 FT-NMR (JEOL LTD.) or JEOL JNM-LA300 FT-NMR (JEOL LTD.; data marked with an asterisk); high-resolution mass spectra (HRMS) were taken with JEOL JMS-GCMATE (JEOL LTD.); and high-performance liquid chromatography (HPLC) was performed with SHIMADZU LC-10A (Shimadzu Corp.).

[0084]

(Example 1) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 4-[1-(4-pyridyl)piperidine] carbaldehyde

A solution of oxalyl chloride (0.43 ml) in anhydrous methylene chloride (20 ml) was cooled to -78°C in a nitrogen atmosphere. To the cooled solution, a solution of anhydrous dimethyl sulfoxide (0.78 ml) in anhydrous methylene chloride (20 ml) was added dropwise over 1 hour. Then, a solution in anhydrous methylene chloride (11 ml) and anhydrous dimethyl sulfoxide (11 ml) of 1-(4-pyridyl)piperidin-4-yl methanol (0.72 g) prepared by a documented (EP 0359389A) method was

added dropwise over 1 hour. After stirring at between -65°C and -60°C for 1 hour, the mixture was cooled to -78°C and triethylamine (2.0 ml) was added. The reaction mixture was stood at room temperature, water was added and extraction with methylene chloride was conducted. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting aldehyde was rather labile and should preferably be used in the next reaction without being purified. It can, however, be analyzed with reasonable accuracy. The above-described treatment was done quickly and the concentrated residue was dissolved in $CDCl_3$ and subjected to NMR measurement; a signal for the proton of aldehyde was identified but disappeared with time.

EIMS: 190 (M^+)

NMR spectrum (*$CDCl_3$) δ ppm: 9.56 (1H, s), 8.16～7.99 (2H, m), 6.82～6.69 (2H, m), 3.83～3.71 (2H, m), 3.02～2.90 (2H, m), 2.61～2.45 (1H, m), 1.90～1.78 (2H, m), 1.52～1.36 (2H, m)

[0085]

<Step 2> Synthesis of 4-[N-[2-(t-butoxycarbonylamino)-1-(ethoxycarbonyl)ethyl]aminomethyl]-1-(4-pyridyl)piperidine borane complex

To a solution in anhydrous methylene chloride (16 ml) of the compound obtained in step 1, β-(t-butoxycarbonylamino)-alanine ethyl ester (0.70 g) prepared by a documented (WO95/11228) method and acetic acid (0.37 ml) were added in that order. After stirring the mixture at room temperature for 30 minutes in a nitrogen atmosphere, sodium triacetoxy-borohydride (1.6 g) was added and the mixture was stirred for one day at room temperature. Water was added to the reaction mixture, which was rendered alkaline with 1 N sodium hydroxide solution and was extracted with methylene chloride. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 95:5) to obtain the titled compound (0.36 g).

NMR spectrum (*$CDCl_3$) δ ppm: 8.18 (2H, d, J=8Hz), 6.69 (2H, d, J=8Hz), 4.95~4.86 (1H, brs), 4.25~4.15 (2H, m), 4.06~3.96 (2H, m), 3.50~3.38 (1H, m), 3.35~3.18 (2H, m), 3.11~2.98 (2H, m), 2.60 (1H, dd, J=7, 12Hz), 2.43~2.34 (1H, m), 2.04 (6H, s), 2.03~1.66 (3H, m), 1.44 (9H, s), 1.30 (3H, t, J=7Hz), 1.30~1.16 (2H, m)

[0086]

<Step 3> Synthesis of 4-[N-bromoacetyl-N-[2-(t-butoxycarbonylamino)-1-(ethoxycarbonyl)ethyl]aminomethyl]-1-(4-pyridyl)piperidine borane complex

A solution in anhydrous methylene chloride (2 ml) of the compound (0.34 g) obtained in step 2 was cooled with ice. To the cooled solution, triethylamine (94 µl) and a solution of bromoacetyl chloride (56 µl) in anhydrous methylene chloride (2 ml) were added in that order and the mixture was stirred at room temperature for 1 hour. After cooling the reaction mixture with ice, water was added and extraction with methylene chloride was conducted. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1 - 95:5) to obtain the titled compound (0.23 g).

NMR spectrum (*$CDCl_3$) δ ppm: 8.22 (2H, d, J=8Hz), 6.72 (2H, d, J=8Hz), 5.20~5.00 (1H, m), 4.26~4.16 (2H, m), 4.15~3.95 (3H, m), 3.89~3.73 (3H, m), 3.55~3.23 (3H, m), 3.18~2.94 (2H, m), 2.20~1.92 (3H, m), 2.04 (6H, s), 1.44 (9H, s), 1.33~1.20 (5H, m)

[0087]

<Step 4> Synthesis of 4-[N-[2-amino-1-(ethoxycarbonyl)ethyl]-N-bromoacetylaminomethyl]-1-(4-pyridyl)piperidine hydrochloride

To the compound (0.21 g) obtained in step 3, 3 N HCl-ethyl acetate (20 ml) was added and the mixture was stirred at room temperature for 2 hours. Ether was added to the reaction mixture and the supernatant was removed by decantation. The same procedure was repeated; ether was added and the supernatant was removed by decantation to give the titled compound (0.17 g).

NMR spectrum (DMSO-d_6) δ ppm: 13.68~13.47 (1H, brs), 8.58~8.32 (3H, brs), 8.28~8.15 (2H, m), 7.35~7.15 (2H, m), 4.59~4.42 (3H, m), 4.42~4.24 (2H, m), 4.18~4.00 (2H, m), 3.52~3.37 (2H, m), 3.37~3.23 (2H, m), 3.23~3.02 (2H, m), 2.17~1.94 (2H, m), 1.92~1.78 (1H, m), 1.38~1.13 (5H, m)

[0088]

<Step 5> Synthesis of 6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

A solution in anhydrous dimethylformamide (5 ml) of the compound (0.16 g) obtained in step 4 was cooled with ice. To the cooled solution, triethylamine (0.41 ml) was added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to

give a crude form of the titled compound, which was used in the next reaction without being purified. A half of the crude product was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 1:1) and NMR spectrum data was taken.

NMR spectrum (*$CDCl_3$) δ ppm: 8.13 (2H, d, J=7Hz), 6.97 (2H, d, J=7Hz), 4.27 (2H, q, J=7Hz), 4.23~4.17 (3H, m), 3.94 (1H, dd, J=8, 14Hz), 3.57 (2H, s), 3.43~3.11 (4H, m), 2.66 (1H, dd, J=7, 14Hz), 2.20~2.03 (1H, m), 1.98~1.81 (2H, m), 1.44~1.24 (2H, m), 1.32 (3H, t, J=7 Hz)

[0089]

<Step 6> Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The remaining half of the crude compound obtained in step 5 was dissolved in anhydrous methylene chloride (5 ml). To the solution, triethylamine (0.1 ml) and 6-chloronaphthalen-2-ylsulfonyl chloride (39.1 mg) were added in that order and the mixture was stirred for one day at room temperature. Water was added to the reaction mixture, which was extracted with methylene chloride. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced

pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 99:1 - 90:10) to yield the titled compound (48 mg).

HRMS: $C_{28}H_{31}ClN_4O_5S$ (M^+): Cal'd 570.1703 Found 570.1681

[0090]

(Example 2) Synthesis of 6-carboxy-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

To a solution in methanol (0.5 ml) of the compound (18 mg) obtained in <step 6> of Example 1, 2 N sodium hydroxide solution (63 µl) was added and the mixture was stirred at 40°C for 30 minutes. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in water and rendered weakly acidic with 0.1 N HCl. The supernatant was removed by decantation and the residue was dissolved in methanol, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to yield the titled compound (9 mg).

[0091]

(Example 3) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-hydroxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound (0.15 g) obtained in <step 6> of Example 1 was dissolved in methanol (10 ml). To the solution, ice-cooled lithium borohydride (0.60 g) was added in three portions at 30-minute intervals. To the reaction mixture, 10% HCl-methanol solution was added under cooling with ice to make it acidic and the mixture was then concentrated to dryness. Water was added to the residue, saturated sodium hydrogencarbonate was then added to make the residue alkaline, and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [NH Silica Gel from Fuji-Silysia Chemical, Ltd.] (eluent; ethyl acetate) to yield the titled compound (60 mg).

[0092]

(Example 4) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methoxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound (43 mg) obtained in Example 3 was suspended in methylene chloride (1 ml). To the stirred suspension, 50% sodium hydroxide solution (0.3 ml) was added under cooling with ice. Then, benzyl triethyl ammonium chloride (3 mg) and

dimethyl sulfate (9 µl) were added and the mixture was stirred for 2 hours under cooling with ice. Ice water was added to the reaction solution to quench the reaction and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to yield the titled compound (16 mg).

[0093]

(Example 5) Synthesis of 6-acetoxymethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound obtained in Example 3 was used as a starting material and acetylated in the usual manner to yield the titled compound.

[0094]

(Example 6) Synthesis of 4-[(E)-4-chlorostyrylsulfonyl]-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

In accordance with the synthesis method of <step 6> in Example 1, the compound obtained in <step 5> of Example 1 was

used as a starting material and reacted with (E)-4-chlorostyrylsulfonyl chloride to yield the titled compound.

[0095]

(Example 7) Synthesis of 6-carboxy-4-[(E)-4-chlorostyrylsulfonyl]-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound obtained in Example 6 was treated in accordance with the method of synthesis in Example 2 to yield the titled compound.

[0096]

(Example 8) Synthesis of 6-aminocarbonyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

Ammonia gas was blown into a solution in 2 N ammonia-methanol (5 ml) of the compound (0.20 g) obtained in <step 6> of Example 1 and the solution was stirred in a fused tube at 80 - 90°C for 8 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to yield the titled compound (0.14 g).

[0097]

(Example 9) Synthesis of 6-aldoximyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-formyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

A solution of oxalyl chloride (33 μl) in anhydrous methylene chloride (1 ml) was cooled to -78°C in a nitrogen atmosphere. To the cooled solution, a solution of anhydrous dimethyl sulfoxide (60 μl) in anhydrous methylene chloride (1 ml) was added dropwise. Then, a solution in anhydrous methylene chloride (1 ml) of the compound (10 mg) obtained in Example 3 was added dropwise. The resulting mixture was stirred at between -65°C and -60°C for 2 hours, then cooled to -78°C and triethylamine (0.16 ml) was added. The reaction mixture was stood at room temperature, water was added and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give a crude form of the titled compound. The compound was used in the next reaction without being purified.

<Step 2> Synthesis of 6-aldoximyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound obtained in step 1 was dissolved in ethanol (1 ml). Hydroxylamine hydrochloride (2.5 mg) and sodium acetate (3 mg) were added to the solution. Acetic acid was added to the reaction mixture to adjust its pH to about 4 and the mixture was stirred for one day at room temperature. The reaction mixture was rendered alkaline by addition of saturated sodium hydrogencarbonate and was extracted with methylene chloride. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [NH Silica Gel from Fuji-Silysia Chemical, Ltd.] (eluent; methylene chloride:methanol = 97:3) to yield the titled compound (1.9 mg).

[0098]

(Example 10) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound (0.20 g) obtained in <step 6> of Example 1 was dissolved in ethanol (5 ml). A solution of lithium

hydroxide monohydrate (15 mg) in water (1 ml) was added and the resulting mixture was heated under reflux for 15 minutes. After concentrating the reaction mixture, thionyl chloride (1 ml) and a small amount of dimethylformamide were added to the residue in that order and the mixture was stirred at room temperature for 40 minutes. After concentrating the reaction mixture, anhydrous methylene chloride (5 ml) was added to the residue and then morpholine (1.5 ml) was added dropwise under cooling with ice. Water was added to the reaction mixture, which was extracted with methylene chloride. The methylene chloride layer was washed with saturated sodium hydrogencarbonate, water and saturated sodium chloride in that order, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [NH Silica Gel from Fuji-Silysia Chemical, Ltd.] (eluent; methylene chloride:methanol = 99:1) to yield the titled compound (0.13 g).

[0099]

(Example 11) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethylaminocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

Using dimethylamine hydrochloride, the method of synthesis in Example 10 was repeated to yield the titled compound.

[0100]

(Example 12) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methoxyaminocarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

To the compound (10 mg) obtained in Example 2, thionyl chloride (0.5 ml) and a small amount of dimethylformamide were added in that order and the mixture was stirred at room temperature for 2 hours. After concentrating the reaction mixture, anhydrous methylene chloride (1 ml) was added to the residue and then a solution of methoxyamine hydrochloride (30 mg) and triethylamine (50 µl) in methylene chloride (1 ml) was added dropwise under cooling with ice. Saturated sodium hydrogencarbonate was added to the reaction mixture, which was then was extracted with methylene chloride. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to yield the titled compound (2.4 mg).

[0101]

(Example 13) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinecarbonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

Using hydroxymethylpiperidine, the method of synthesis in Example 10 was repeated to yield the titled compound.

[0102]

(Example 14) Synthesis of 6-aminomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-phthaliminomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

DEAD (as 40% toluene solution) (1.71 ml) was added to a solution of triphenyl phosphine (0.99 g) and phthalimide (0.56 g) in anhydrous methylene chloride (30 ml) under cooling with ice. After stirring the mixture at the same temperature for 10 minutes, the compound (0.50 g) obtained in Example 3 was added and the mixture was stirred at room temperature for 30 minutes. Saturated sodium hydrogencarbonate was added to the reaction mixture under cooling with ice, followed by extraction with methylene chloride, washing with saturated sodium chloride, drying with anhydrous sodium sulfate and

distilling off the solvent under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to give the titled compound (0.61 g).

NMR spectrum ($CDCl_3$) δ ppm: 8.42 (1H, s), 8.24~8.19 (2H, m), 7.97~7.87 (6H, m), 7.83~7.75 (2H, m), 7.63~7.57 (1H, m), 6.62~6.56 (2H, m), 4.33~4.20 (1H, m), 4.11 (1H, d, J=17Hz), 4.04~3.93 (2H, m), 3.87~3.68 (4H, m), 3.43 (1H, d, J=17Hz), 2.96~2.68 (4H, m), 2.08~1.87 (1H, m), 1.73~1.57 (2H, m), 1.42~1.17 (2H, m)

<Step 2> Synthesis of 6-aminomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

A portion (0.61 g) of the compound obtained in step 1 was suspended in ethanol (15 ml). Hydrazine monohydrate (54 µl) was added to the suspension at room temperature, followed by stirring at room temperature for 20 hours. The suspension was then allowed to reflux for 4 hours. After leaving the suspension to cool, the insolubles were filtered off and the filtrate was concentrated. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to yield the titled compound (0.36 g).

[0103]

(Example 15) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6- (4-methylbenzenesulfonyl)oxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

A portion (50 mg) of the compound obtained in Example 3 was suspended in methylene chloride (1 ml). To the stirred suspension, triethylamine (0.3 ml) and 4-methylbenzenesulfonyl chloride (20 mg) were added in that order under cooling with ice and the mixture was stirred for one day at room temperature. Ice water was added to the reaction solution to quench the reaction and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 95:5) to give the titled compound (52 mg).

NMR spectrum (*$CDCl_3$) δ ppm: 8.34 (1H, s), 8.25~8.20 (2H, m), 7.98~7.92 (3H, m), 7.83 (2H, d, J=9Hz), 7.76 (1H, dd, J=2, 9Hz), 7.65~7.60 (1H, m), 7.41 (2H, d, J=9 Hz), 6.62~6.57 (2H, m), 4.23~4.05 (4H, m), 3.90~3.67 (4H, m), 3.31 (1H, d, J=17Hz), 2.80~2.62 (4H, m), 2.48

(3H, s), 1.98～1.84 (1H, m), 1.76～1.45 (2H, m), 1.36～1.16 (2H, m)

<Step 2> Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-morpholinomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound (100 mg) obtained in step 1 was dissolved in anhydrous dimethylformamide (2 ml). Potassium carbonate (100 mg) and morpholine (128 µl) were successively added to the solution, which was then stirred at 80°C for 4 hours. Ice water was added to the reaction solution to quench the reaction and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 95:5) to yield the titled compound (36 mg).

[0104]

(Example 16) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-dimethylaminomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

A portion (31.3 mg) of the compound obtained in <step 2> of Example 14 and paraformaldehyde (4.9 mg) were suspended in

anhydrous methylene chloride (1 ml). To the suspension, acetic acid (13.6 µl) and sodium triacetoxyborohydride (50.2 mg) were added at room temperature and the mixture was stirred at room temperature for 20 hours. Saturated sodium hydrogencarbonate was added to the reaction mixture under cooling with ice and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to yield the titled compound (11.6 mg).

[0105]

(Example 17) Synthesis of 6-acetamidomethyl-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound obtained in Example 14 was used as a starting material and acetylated in the usual manner to yield the titled compound.

[0106]

(Example 18) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-methanesulfonylamidomethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound obtained in Example 14 was used as a starting material and methanesulfonylated in the usual manner to yield the titled compound.

[0107]

(Example 19) Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinemethyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 4-(t-butyldimethylsiloxy) piperidine

To a stirred solution of 4-hydroxypiperidine (2.0 g) in anhydrous methylene chloride (20 ml), pyridine (1.9 ml) and t-butyldimethylsilyl trifluoromethanesulfonate (5.0 ml) were successively added under cooling with ice and the resulting mixture was stirred for 3 hours. Ice water was added to the reaction solution to quench the reaction and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 95:5) to give the titled compound (3.8 g).

NMR spectrum (*$CDCl_3$) δ ppm: 4.13~4.05 (1H, m), 3.44~3.20 (4H, m), 2.10~1.96 (2H, m), 1.82~1.70 (2H, m), 0.89 (9H, s), 0.07 (6H, s)

<Step 2> Synthesis of 6-[4-(t-butyldimethylsiloxy) piperidinemethyl]-4-(6-chloronaphthalen-2-ylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound (0.30 g) obtained in <step 1> of Example 15 was dissolved in anhydrous dimethylformamide (2 ml). Potassium carbonate (0.60 g) and a portion (0.47 g) of the compound obtained in <step 1> of Example 19 were added in that order and the mixture was stirred at 80°C for 2.5 hours. Potassium carbonate (0.60 g) and the compound (0.47 g) obtained in <step 1> of Example 19 were further added and the mixture was stirred at 80°C for 6 hours. Ice water was added to the reaction solution to quench the reaction and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 95:5) and on [NH Silica Gel from Fuji-Silysia Chemical, Ltd.] (eluent; ethyl acetate) to give the titled compound (0.15 g). NMR spectrum (*$CDCl_3$) δ ppm: 8.36 (1H, s), 8.23~8.18 (2H, m), 7.98~7.92 (3H, m), 7.83~7.78 (1H, m), 7.61 (1H, dd, J=2, 9Hz), 6.60~6.55 (2H, m), 4.23~4.08 (2H, m), 3.91~3.64 (4H, m), 3.31 (1H, d, J=17Hz), 3.29~3.2

2 (1H, m), 2. 80～2. 55 (7H, m), 2. 42～2. 21 (3H, m), 2. 02～1. 12 (9H, m), 0. 89 (9H, s), 0. 05 (6H, s)

<Step 3> Synthesis of 4-(6-chloronaphthalen-2-ylsulfonyl)-6-(4-hydroxypiperidinemethyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound (0. 15 g) obtained in step 2 was dissolved in tetrahydrofuran (2 ml). Tetrabutylammonium fluoride (as 1.0 M tetrahydrofuran solution) (0.25 ml) was added and the mixture was stirred for one day at room temperature. Ice water was added to the reaction solution to quench the reaction and extraction with methylene chloride was conducted. The methylene chloride layer was washed with saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography [NH Silica Gel from Fuji-Silysia Chemical, Ltd.] (eluent; ethyl acetate) to yield the titled compound (58 mg).

[0108]

(Example 20) Synthesis of 4-(2-naphthylsulfonyl)-6-hydroxymethyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

Using 2-naphthalenesulfonyl chloride, the method of synthesis in Example 3 was repeated to yield the titled compound.

[0109]

(Example 21) Synthesis of 6-acetoxymethyl-4-(2-naphthylsulfonyl)-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

The compound obtained in Example 20 was used as a starting material and acetylated in the usual manner to yield the titled compound.

[0110]

(Example 22) Synthesis of (R)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

<Step 1> Synthesis of 1-(4-pyridyl)piperidine-4-carbaldehyde

A solution of oxalyl chloride (2.45 ml) in anhydrous methylene chloride (100 ml) was cooled to -78°C in a nitrogen atmosphere. To the cooled solution, a solution of anhydrous dimethyl sulfoxide (4.44 ml) in anhydrous methylene chloride (100 ml) was added dropwise over 1 hour. Then, a solution in anhydrous methylene chloride (50 ml) and anhydrous dimethyl sulfoxide (50 ml) of 1-(4-pyridyl)piperidin-4-yl methanol (4.14 g) prepared by a documented (EP 0359389) method was added dropwise over 1 hour. After stirring at between -65°C and -60°C for 1 hour, the mixture was cooled to -78°C and triethylamine (11.4 ml) was added. The reaction mixture was

stood at room temperature, water was added and extraction with methylene chloride was conducted. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The resulting aldehyde was rather labile, so it was used in the next reaction without being purified.

EIMS: 190 (M^+)

NMR spectrum (*$CDCl_3$) δ ppm: 9.56 (1H, s), 8.16～7.99 (2H, m), 6.82～6.69 (2H, m), 3.83～3.71 (2H, m), 3.02～2.90 (2H, m), 2.61～2.45 (1H, m), 1.90～1.78 (2H, m), 1.52～1.36 (2H, m)

[0111]

<Step 2> Synthesis of (R)-4-[N-[2-(t-butoxycarbonylamino)-1-(ethoxycarbonyl)ethyl]aminomethyl]-1-(4-pyridyl)piperidine borane complex

To a solution in anhydrous methylene chloride (90 ml) of the compound obtained in step 1, (R)-β-(t-butoxycarbonyl-amino)alanine ethyl ester (4.00 g) prepared by a documented (WO95/11228) method and acetic acid (2.11 ml) were added in that order. After stirring the mixture at room temperature for 30 minutes, sodium triacetoxyborohydride (9.12 g) was added and the mixture was stirred at room temperature for 2

days. The reaction mixture was cooled with ice and, after adding water, it was extracted with methylene chloride. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to give a crude form of the titled compound (5.73 g).

NMR spectrum (*$CDCl_3$) δ ppm: 8.18 (2H, d, J=8Hz), 6.69 (2H, d, J=8Hz), 4.95~4.86 (1H, brs), 4.25~4.15 (2H, m), 4.06~3.96 (2H, m), 3.50~3.38 (1H, m), 3.35~3.18 (2H, m), 3.11~2.98 (2H, m), 2.60 (1H, dd, J=7, 12Hz), 2.43~2.34 (1H, m), 2.04 (6H, s), 2.03~1.66 (3H, m), 1.44 (9H, s), 1.30 (3H, t, J=7Hz), 1.30~1.16 (2H, m)

[0112]

<Step 3> Synthesis of (R)-4-[N-bromoacetyl-N-[2-(t-butoxycarbonylamino)-1-(ethoxycarbonyl)ethyl]aminomethyl]-1-(4-pyridyl)piperidine borane complex

A solution in anhydrous methylene chloride (100 ml) of the compound (5.41 g) obtained in step 2 was cooled with ice. To the cooled solution, triethylamine (3.00 ml) and a solution of bromoacetyl chloride (1.77 ml) in anhydrous methylene chloride (20 ml) were added in that order and the mixture was stirred at room temperature for 1 hour. After cooling the reaction mixture with ice, water was added and extraction with methylene chloride was conducted. The methylene chloride

layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 97:3) to give the titled compound (2.94 g).

NMR spectrum (*$CDCl_3$) δ ppm: 8.22 (2H, d, J=8Hz), 6.72 (2H, d, J=8Hz), 5.20~5.00 (1H, m), 4.26~4.16 (2H, m), 4.15~3.95 (3H, m), 3.89~3.73 (3H, m), 3.55~3.23 (3H, m), 3.18~2.94 (2H, m), 2.20~1.92 (3H, m), 2.04 (6H, s), 1.44 (9H, s), 1.33~1.20 (5H, m)

[0113]

<Step 4> Synthesis of (R)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

A solution in dry methanol (30 ml) of a portion (2.90 g) of the compound obtained in step 3 was cooled with ice and 10% HCl-methanol (30 ml) was added dropwise. The resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was concentrated, the residue was dissolved in anhydrous dimethylformamide (30 ml) and triethylamine (6.0 ml) was added dropwise under cooling with ice. The reaction mixture was stirred for one day at room temperature; under cooling with ice, a solution of triethylamine (3.0 ml) in

anhydrous methylene chloride (10 ml) and then a solution of 6-chloronaphthalen-2-ylsulfonyl chloride (1.13 g) in anhydrous methylene chloride (10 ml) were added dropwise, and the mixture was stirred for one day at room temperature. The reaction mixture was cooled with ice and, after adding water, it was extracted with methylene chloride. The methylene chloride layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; methylene chloride:methanol = 90:10) to yield the titled compound (0.92 g). The optical purity of this compound was measured by HPLC [CHIRALPAK™ AD (DAICEL CHEMICAL INDUSTRIES, LTD.); hexane:isopropanol:diethylamine = 6:4:0.04] and it was found to be 98.3% e.e.

HRMS: $C_{28}H_{31}ClN_4O_5S$ (M^+): Cal'd 570.1703 Found 570.1664

[0114]

(Example 23) Synthesis of (S)-4-(6-chloronaphthalen-2-ylsulfonyl)-6-ethoxycarbonyl-1-[1-(4-pyridyl)piperidin-4-ylmethyl]piperazin-2-one

Using (S)-β-(t-butoxycarbonylamino)alanine ethyl ester, the method of synthesis in Example 22 was repeated to yield the titled compound. The optical purity of this compound was

measured by HPLC [CHIRALPACK™ AD (DAICEL CHEMICAL INDUSTRIES, LTD.); hexane:isopropanol:diethylamine = 6:4:0.04] and it was found to be 97.7% e.e.

[0115]

Examples 24 - 46 correspond to methanesulfonates (mono-salts) of the compounds synthesized in Examples 1 - 23, respectively. The methanesulfonates were similarly synthesized and confirmed.

The NMR data for the typical compounds synthesized in the Examples are shown in Figs. 3 - 5.

The structures of the compounds synthesized in the Examples 1 - 23 of the present invention were shown in Figs. 1 - 2. The structures of the compounds (salts) synthesized in Examples 24 - 46 are not shown.

[0116]

[Effects of the Invention]

The compounds of the present invention are a specific FXa inhibitor and have a potent anticoagulation effect. They are, therefore, useful as anticoagulants or as preventives or therapeutics of diseases caused by thrombus or embolus. Examples of such diseases for which the compounds of the present invention are indicated include diseases from ischemic cerebrovascular disorders such as cerebral thrombosis,

cerebral infarction, cerebral embolism and transient cerebral ischemic attacks (TIA), diseases associated with ischemic heart diseases such as acute or chronic myocardial infarction, unstable angina pectoris and coronary thrombolysis, diseases from pulmonary infarction, pulmonary embolism and other conditions of pulmonary angiopathy, and diseases from various cases of angiopathy including peripheral arterial obstruction, deep venous thrombosis, disseminated intravascular coagulation (DIC), thrombosis after artificial blood vessel or heart valve replacement, reocclusion and restenosis following coronary artery bypass surgery, reocclusion and restenosis on or after PTCA, and thrombosis on extracorporeal circulation of blood.

The compounds of the present invention are also useful as preventives or therapeutics of infections with influenza virus.

[BRIEF DESCRIPTION OF THE DRAWINGS]

[Fig. 1] This shows structural formulae of the compounds synthesized in the Examples 1 - 12 of the present invention.

[Fig. 2] This shows structural formulae of the compounds synthesized in the Examples 13 - 23 of the present invention.

[Fig. 3] This shows NMR data on the compounds synthesized in the Examples of the present invention.

[Fig. 4] This shows NMR data on the compounds synthesized in the Examples of the present invention.

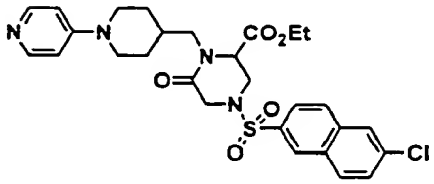
[Fig. 5] This shows NMR data on the compounds synthesized in the Examples of the present invention.

Japanese Patent Application No.10-311491

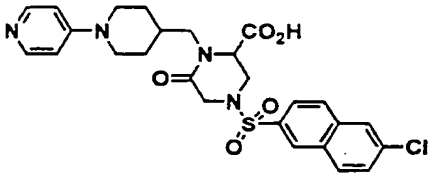
【TYPE OF THE DOCUMENT】Drawings

【FIG.1】

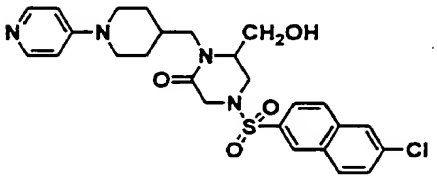
Example 1



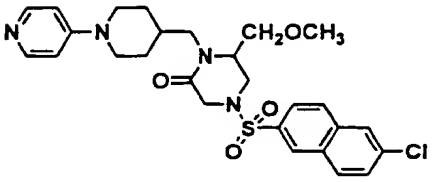
Example 2



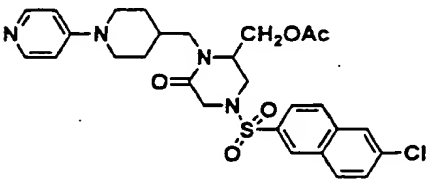
Example 3



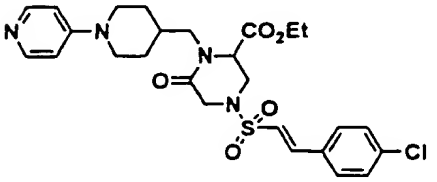
Example 4



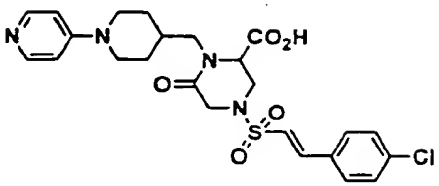
Example 5



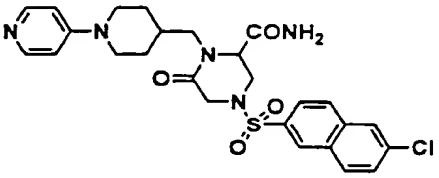
Example 6



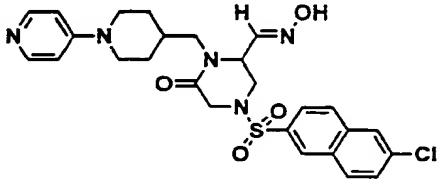
Example 7



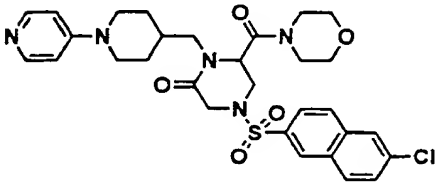
Example 8



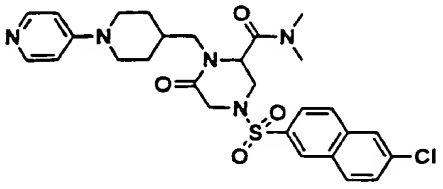
Example 9



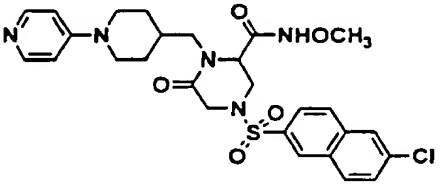
Example 10



Example 11

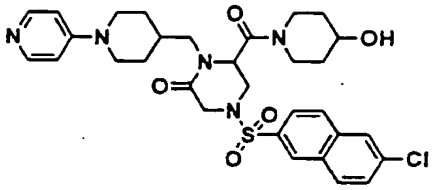


Example 12

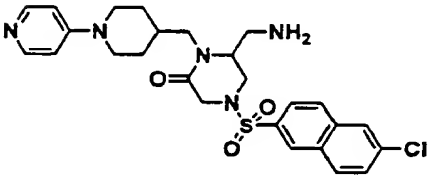


【FIG.2】

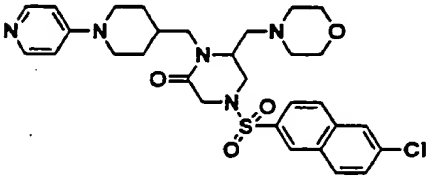
Example 13



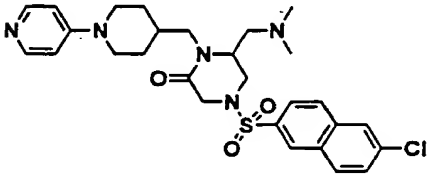
Example 14



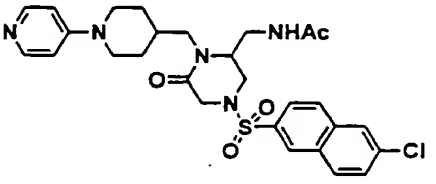
Example 15



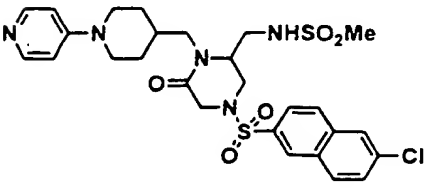
Example 16



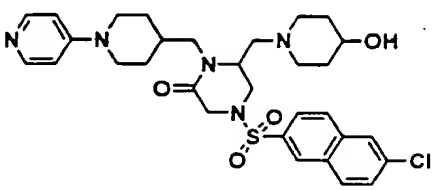
Example 17



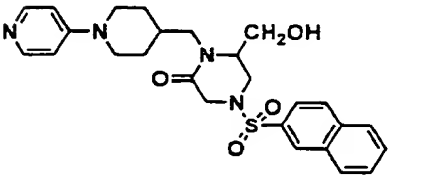
Example 18



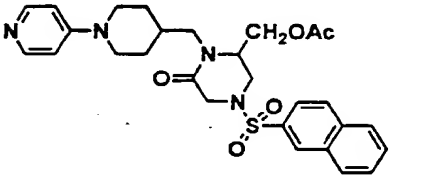
Example 19



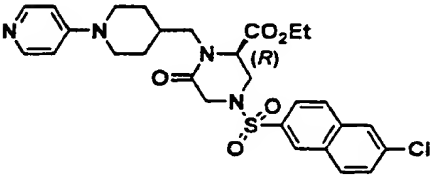
Example 20



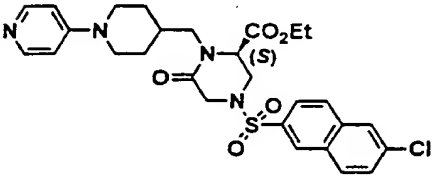
Example 21



Example 22



Example 23



【FIG.3】

Ex. No.	NMR (ppm) (* : 300MHz, Without asterisk : 270MHz)
1	CDCl3:8.34 (1H, s), 8.25-8.18 (2H, m), 7.98-7.90 (3H, m), 7.77 (1H, dd, J=2, 9Hz), 7.64-7.58 (1H, m), 6.64-6.57 (2H, m), 4.38-4.04 (5H, m), 3.96-3.75 (3H, m), 3.46 (1H, d, J=17Hz), 3.07-2.96 (1H, m), 2.88-2.68 (2H, m), 2.66-2.55 (1H, m), 1.93-1.75 (1H, m), 1.73-1.55 (2H, m), 1.32 (3H, t, J=7Hz), 1.32-1.14 (2H, m)
2	CD3OD*:8.47 (1H, s), 8.16-7.99 (5H, m), 7.90-7.83 (1H, m), 7.64 (1H, dd, J=2, 9Hz), 7.02 (2H, d, J=8Hz), 4.18-3.91 (5H, m), 3.81 (1H, dd, J=8, 14Hz), 3.58 (1H, d, J=16Hz), 3.30-3.20 (1H, m), 3.12-2.93 (2H, m), 2.72 (1H, dd, J=7, 14Hz), 2.08-1.92 (1H, m), 1.82-1.71 (1H, m), 1.62-1.52 (1H, m), 1.31-1.04 (2H, m)
3	CDCl3:8.36 (1H, s), 8.21 (2H, d, J=7Hz), 8.00-7.90 (3H, m), 7.84-7.76 (1H, m), 7.62 (1H, dd, J=2, 9Hz), 6.58 (2H, d, J=7Hz), 4.28-4.12 (2H, m), 3.95-3.72 (5H, m), 3.48-3.35 (2H, m), 2.84-2.63 (4H, m), 2.05-1.46 (3H, m), 1.34-1.13 (2H, m)
4	CDCl3*:8.36 (1H, s), 8.26-8.19 (2H, m), 7.98-7.92 (3H, m), 7.80 (1H, dd, J=2, 9Hz), 7.61 (1H, dd, J=2, 9Hz), 6.62-6.55 (2H, m), 4.17 (1H, d, J=17Hz), 4.05 (1H, d, J=12Hz), 3.94-3.70 (3H, m), 3.70-3.43 (3H, m), 3.38 (3H, s), 3.38 (1H, d, J=17Hz), 2.88-2.66 (4H, m), 2.08-1.90 (1H, m), 1.71-1.54 (2H, m), 1.38-1.07 (2H, m)
5	CDCl3:8.37 (1H, s), 8.23-8.19 (2H, m), 7.98-7.93 (3H, m), 7.80 (1H, dd, J=2, 9Hz), 7.62 (1H, dd, J=2, 9Hz), 6.60-6.56 (2H, m), 4.40-4.33 (1H, m), 4.25-4.11 (2H, m), 4.04 (1H, d, J=12Hz), 3.95-3.74 (3H, m), 3.61-3.50 (1H, m), 3.38 (1H, d, J=17Hz), 2.88-2.67 (4H, m), 2.10 (3H, s), 2.03-1.86 (1H, m), 1.70-1.55 (2H, m), 1.38-1.16 (2H, m)

【FIG.4】

Ex. No.	NMR (ppm) (* : 300MHz, Without asterisk : 270MHz)
6	CDCl3*:8.27-8.19 (2H, m), 7.47 (1H, d, J=15Hz), 7.47-7.38 (4H, m), 6.67-6.60 (2H, m), 6.59 (1H, d, J=15Hz), 4.28-4.07 (5H, m), 4.00-3.82 (3H, m), 3.73 (1H, d, J=17Hz), 3.32 (1H, dd, J=4, 13Hz), 2.89-2.75 (2H, m), 2.67 (1H, dd, J=8, 14Hz), 2.00-1.63 (3H, m), 1.40-1.20 (2H, m), 1.30 (3H, t, J=7Hz)
7	CD3OD*:8.08-8.02 (2H, m), 7.69-7.63 (1H, m), 7.52-7.37 (4H, m), 7.17-7.00 (3H, m), 4.29-4.10 (2H, m), 4.09-3.75 (4H, m), 3.62-3.02 (4H, m), 2.90-2.73 (1H, m), 2.21-2.05 (1H, m), 1.95-1.73 (2H, m), 1.43-1.12 (2H, m)
14	CDCl3*:8.36 (1H, d, J=1Hz), 8.22-8.19 (2H, m), 7.97-7.94 (3H, m), 7.82-7.78 (1H, m), 7.61 (1H, dd, J=2, 9Hz), 6.59-6.57 (2H, m), 4.25-4.16 (2H, m), 3.89-3.76 (3H, m), 3.36 (1H, d, J=17Hz), 3.30-3.22 (1H, m), 3.07 (1H, dd, J=10, 13Hz), 2.96 (1H, dd, J=4, 13Hz), 2.79-2.68 (3H, m), 2.63 (1H, dd, J=8, 14Hz), 2.05-1.87 (1H, m), 1.73-1.57 (2H, m), 1.35-1.14 (2H, m)
15	CDCl3*:8.36 (1H, d, J=2Hz), 8.21 (2H, dd, J=2, 5Hz), 7.97-7.93 (3H, m), 7.81 (1H, dd, J=2, 9Hz), 7.64-7.60 (1H, m), 6.58 (2H, dd, J=2, 5Hz), 4.26 (1H, d, J=10Hz), 4.21 (1H, d, J=15Hz), 3.94-3.64 (7H, m), 3.35-3.24 (2H, m), 2.91-2.52 (9H, m), 2.46-2.36 (1H, m), 2.12-1.87 (1H, m), 1.68-1.57 (2H, m), 1.37-1.14 (2H, m)

【FIG.5】

Ex. No.	NMR (ppm) (* : 300MHz, Without asterisk : 270MHz)
16	CDCl3*:8.36 (1H, s), 8.21 (2H, d, J=6Hz), 7.96-7.93 (3H, m), 7.81 (1H, dd, J=2, 9Hz), 7.63-7.59 (1H, m), 6.58 (2H, d, J=6Hz), 4.23-4.18 (2H, m), 3.89-3.76 (3H, m), 3.29 (1H, d, J=17Hz), 3.30-3.21 (1H, m), 2.87-2.55 (5H, m), 2.38-2.24 (1H, m), 2.31 (6H, s), 2.04-1.87 (1H, m), 1.72-1.57 (2H, m), 1.34-1.16 (2H, m)
19	CDCl3*:8.36 (1H, s), 8.25-8.18 (2H, m), 7.99-7.92 (3H, m), 7.86-7.78 (1H, m), 7.66-7.58 (1H, m), 6.62-6.56 (2H, m), 4.25-4.08 (2H, m), 3.93-3.62 (4H, m), 3.36-3.22 (2H, m), 2.90-2.54 (7H, m), 2.44-2.20 (3H, m), 2.10-1.10 (9H, m)
22	CDCl3:8.34 (1H, s), 8.25-8.18 (2H, m), 7.98-7.90 (3H, m), 7.77 (1H, dd, J=2, 9Hz), 7.64-7.58 (1H, m), 6.64-6.57 (2H, m), 4.38-4.04 (5H, m), 3.96-3.75 (3H, m), 3.46 (1H, d, J=17Hz), 3.07-2.96 (1H, m), 2.88-2.68 (2H, m), 2.66-2.55 (1H, m), 1.93-1.75 (1H, m), 1.73-1.55 (2H, m), 1.32 (3H, t, J=7Hz), 1.32-1.14 (2H, m)
23	CDCl3:8.34 (1H, s), 8.25-8.18 (2H, m), 7.98-7.90 (3H, m), 7.77 (1H, dd, J=2, 9Hz), 7.64-7.58 (1H, m), 6.64-6.57 (2H, m), 4.38-4.04 (5H, m), 3.96-3.75 (3H, m), 3.46 (1H, d, J=17Hz), 3.07-2.96 (1H, m), 2.88-2.68 (2H, m), 2.66-2.55 (1H, m), 1.93-1.75 (1H, m), 1.73-1.55 (2H, m), 1.32 (3H, t, J=7Hz), 1.32-1.14 (2H, m)

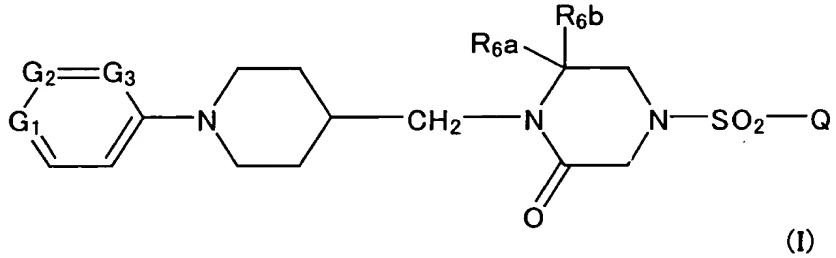
[TYPE OF THE DOCUMENT] Abstract

[ABSTRACT]

[Subject] There are provided orally administrable aromatic compounds having cyclic amino groups or salts thereof that are useful as pharmaceuticals, particularly as an inhibitor of activated blood coagulation factor X (hereunder referred to as FXa), and which show potent anticoagulation action.

[Means for Solution] A compound represented by the following formula (I) or a salt thereof, and a pharmaceutical composition containing it as an active ingredient:

[Chemical Formula 1]



(I)

[Selected Drawing] None